



having seen the disease in an elderly Indian who had been taking large quantities of quinacrine hydrochloride at the suggestion of some of his American soldier friends.

Of the group of 60 cases which we are reporting, 28 were discovered only by diligent search and by publicity among the medical officers, since the eruption was not sufficiently extensive to warrant hospitalization. The remaining 32 were observed from time to time in hospitals and dispensaries on consultation. This statement is stressed because it illustrates the general lack of intense or severe symptoms of this disease. The eruption in the men all followed more or less the general pattern previously described, and on the basis of extension of the eruption they were divided into three groups as follows:

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#### RESULTS OF SURVEY

A survey of cases of atypical lichenoid dermatitis was made by means of an examination sheet and questionnaire in which location and type of eruption were recorded. This is similar to an analysis sheet used by Ambler in his survey for the United States Army. A further analysis of these questionnaires revealed the following significant data:

1. *Age*.—The eruption occurred predominantly among the older men, most cases occurring in the age group between 35 and 45 years. The average age for occurrence of the eruption was 35 years.

2. *Distribution of Eruption*.—The eruption occurred predominantly on the dorsa of the feet and hands and legs, all patients having it in one or more of these areas. In over half of the cases it occurred on the eyelids, and in 40 per cent the eruption was on the lips and mouth. Only 1 per cent had even a mild generalized exfoliation.

3. *Type of Eruption and Degree of Involvement*.—Since most of the patients had eruptions on the feet and hands, 90 per cent were classified as having eczematoid reactions with their eruptions. Over half the patients had lichenoid and hypertrophic lesions, but only 4 per cent had a diffuse follicular keratosis and 2 per cent atrophy and alopecia or ulcerations.

4. *Relation to Quinacrine Hydrochloride*.—All patients had been taking quinacrine hydrochloride in routine malaria-suppressive doses of 2 tablets daily, and some had been overzealous and taken more. The yellow color of the skin was predominant in all, more so; of course, in the brunettes. Since it was obligatory to evacuate these men to the United States, we had only a meager opportunity to observe the effects of discontinuance of use of quinacrine hydrochloride. However, it was the general opinion that improvement was parallel to the discontinuance of the use of quinacrine hydrochloride, and in 4 cases we believed that

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exfoliative dermatitis. This has been substantiated by reports from the South Pacific.<sup>11</sup> But it is equally obvious that prolonged ingestion of quinacrine hydrochloride in unusual circumstances will produce a chronic "fixed type" of drug eruption of bizarre type, which has some clinical similarities to lichen planus. It is to this type of cutaneous disease which the redundant and unsatisfactory term "atypical lichenoid dermatitis" has by common consent been attached.

Since it is likely that American men in the future will be occasionally exposed to malaria in tropical countries and be obliged to take quinacrine hydrochloride for prevention of the symptoms of malaria, obscure cases of this drug eruption may be occasionally observed, but it is sincerely hoped that there will not occur again any necessity for administration of quinacrine hydrochloride in such quantities under such difficult living conditions and that atypical lichenoid dermatitis will be only a distasteful memory and a cutaneous disease of the past.

#### SUMMARY

1. Atypical lichenoid dermatitis is essentially a chronic progressive, relatively mild cutaneous eruption which occurred among military personnel in World War II and which resembles lichen planus in some of its clinical features.
2. The ingestion of relatively large quantities of quinacrine hydrochloride over long periods is a major factor in its production.
3. It appears to be a drug eruption of the "fixed type" and should be distinguished from the acute eruptions due to idiosyncrasy to quinacrine hydrochloride.

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#### ABSTRACT OF DISCUSSION

DR. MARION B. SULZBERGER, New York: I am grateful for this opportunity to open the discussion on Dr. Alden's excellent paper. Dr. Alden has seen more cases of this dermatosis than I have, and I certainly cannot add anything concerning the clinical manifestations, with perhaps one exception. Some of the patients with reactions to quinacrine hydrochloride (atabrine) whom I saw presented lesions which strongly resembled Riehl's melanosis or dermatitis lichenoides et bullous toxica of Erich Hoffman or poikiloderma of Civatte. They had all the lichenoid, pigmentary, atrophic, telangiectatic and poikiloderma-like changes seen in these diseases. Of course, the disorders in the cases Dr. Barksdale, Dr. Bianco and I saw at Bethesda, Md., were probably in much later stages, the patients being seen at a much longer interval after the last ingestion of quinacrine hydrochloride than those that were seen in the field by Dr. Alden. It is perhaps

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Following Prolonged Atabrine Administration and Resembling Brill's Typhus Fever: Report of a Case, J. M. A. Georgia **27**:317 (Aug.) 1938. Noojin, R. O., and Callaway, J. L.: Generalized Exfoliative Erythroderma Following Atabrine: Report of a Case, North Carolina M. J. **3**:239 (May) 1942.

11. Schmitt.<sup>1</sup> Nisbet.<sup>4a</sup> Bagby and others.<sup>4b</sup> Footnote 8.



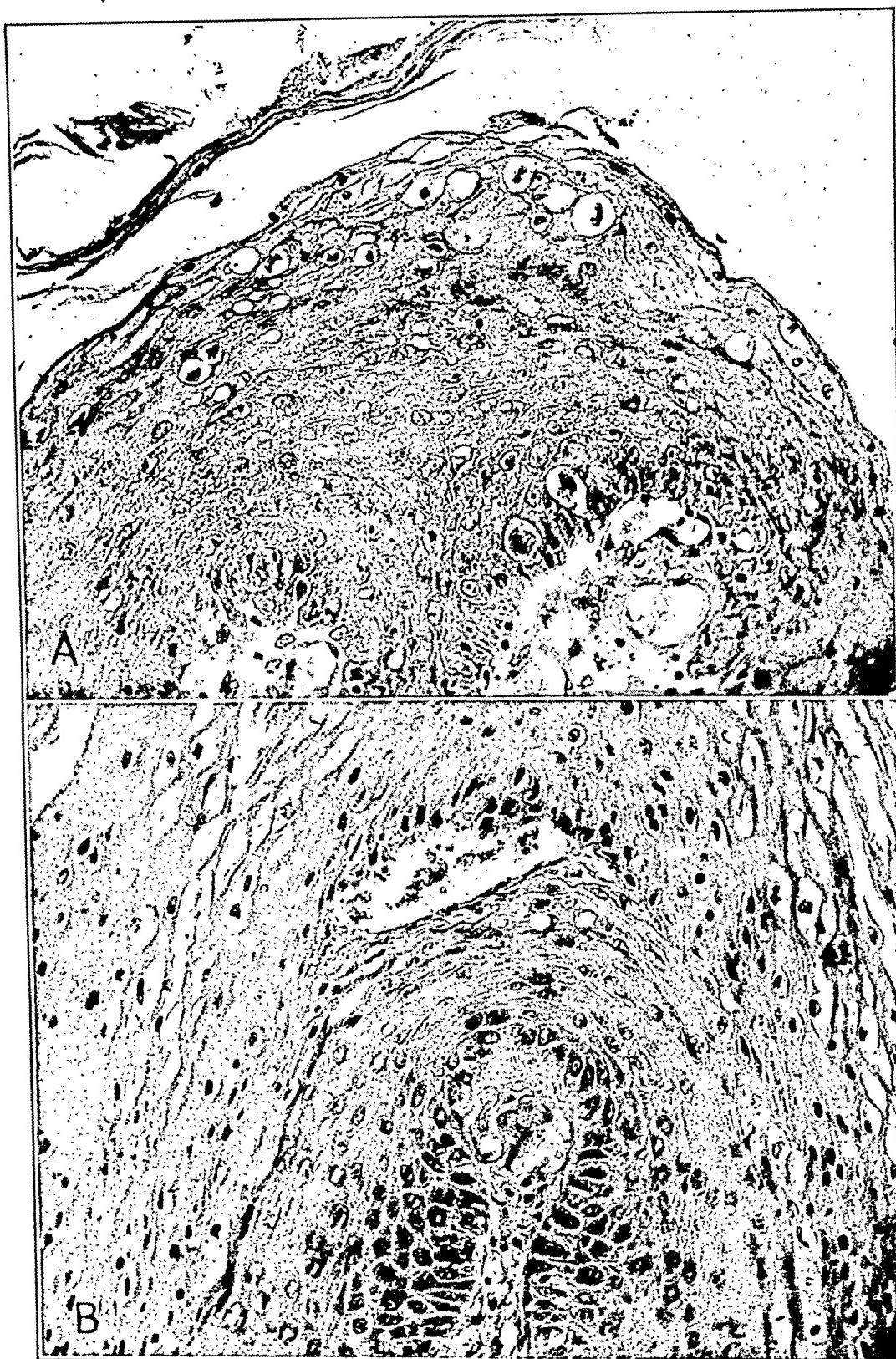


Fig. 7.—*A*, condyloma acuminatum twenty-four hours after a single application of resin of *podophyllum* in oil. There is widespread degeneration in the upper portion, while in the basal portions are some "podophyllin cells" and extensive but less striking nuclear alterations.  $\times 113$ . *B*, condyloma acuminatum twenty-four hours after application of salicylic acid. The superficial portions have a "fixed" appearance and are sharply demarcated from the underlying well preserved epithelium. A vesicle is present at the line of demarcation. Note the small hyaline thrombus.  $\times 170$ .

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4. There are two disadvantages to Kaplan's otherwise excellent method of treatment. 1. The resin of podophyllum in oil has a spreading effect and cannot be confined to the condylomas; irritation to the normal mucosa results. 2. A liquid petrolatum suspension of a resinous mixture would not be expected to be penetrating. To overcome these disadvantages it is recommended that a solution of 20 per cent resin of podophyllum in 95 per cent alcohol be used instead of the suspension in oil. Thirty patients with condylomata acuminata were treated with the alcoholic solution, and much less irritation to the normal mucosa occurred. Fifteen per cent cures of one hundred verrucae vulgares resulted from applications of 20 per cent resin of podophyllum in 95 per cent alcohol.

5. The dramatic response of condylomata acuminata to resin of podophyllum cannot be explained on the basis of Culp and Kaplan's<sup>14</sup> theory that the drug produces a spasm of the small vessels, which in turn produces ischemia, necrosis and sloughing. The main effect of resin of podophyllum appears to be directly on the epithelial cells. Two types of action are manifest. One is of direct degenerative character, while the other is the production of bizarre cell forms interpreted as distorted mitotic figures. These forms, which are called "podophyllin cells," are similar to so-called colchicine figures.<sup>15</sup> It appears that resin of podophyllum exerts a profound and subtle action on cell metabolism, in contrast to salicylic or trichloroacetic acid which produces a simple "fixing" or coagulation effect.

6. Podophyllotoxin is easily susceptible to alkaline hydrolysis.<sup>4</sup> Solutions of resin of podophyllum in sodium and potassium hydroxide proved inert when applied to condylomata acuminata, indicating that podophyllotoxin is probably the substance in resin of podophyllum responsible for its cytotoxic effect.

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#### ABSTRACT OF DISCUSSION

DR. HAROLD N. COLE, Cleveland: This is one of the situations in which the discusser does not have much to say. I wish to congratulate these men for the nice piece of work they have done with a simple disease, condylomata acuminata, actually bringing out the real causative effect of the resin of podophyllum on the cell itself, causing it to be destroyed, and showing that it is not due to a disturbance of the blood supply. I have a profound respect for these workers who have been able, despite the heavy duties of a large military hospital, to carry on such a scholarly investigation and that, too, to its complete solution.

DR. HARTHER L. KEIM, Detroit: That resin of podophyllum will irritate the skin is attested to by persons who work with this drug. Just a week ago I saw an obese woman who handled resin of podophyllum in its manufacture and who had extensive severe dermatitis, particularly in the cubital fossae. Evidently

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DR. PAUL E. BECHET, Elizabeth, N. J.: I have used electrocoagulation for a few years, but unfortunately recurrences do at times occur; one must be careful to avoid scarring, which at times is a difficult thing to do when the lesions are numerous. If the method proposed by Dr. Sullivan and Dr. King prevents recurrences and causes no scarring, it should supersede electrodesiccation, which, besides the faults enumerated, is somewhat painful.

DR. FRANK J. EICHENLAUB, Washington, D. C.: When this new treatment proved so efficacious for condyloma acuminatum, it was my hope that it might work on the common wart elsewhere. Local application failed to work. I therefore injected a few drops of alcoholic extract of resin of podophyllum in the base of each wart, on the theory that the drug was not penetrating. However, even with this type of treatment, the only effect was a necrosis of tissue around the wart, with no effect on the wart itself.

DR. GEORGE C. ANDREWS, New York: Although I agree with those who say that resin of podophyllum does not affect common warts, I have had excellent results in some plantar warts and in warts on the bearded region. I will recite the case of a patient whom I treated for five years for plantar warts. I desiccated them and treated them with roentgen rays, I treated them with radium and I gave injections of bismuth preparations, solid carbon dioxide and every drug I could suggest. He came in again with five plantar warts, and I tried the resin of podophyllum in oil. I painted it on and gave him some to paint on every day for a week. Inside of a week or two they were entirely gone.

I have used it on several other patients with plantar warts, with success. I do not say that it will remove more than 25 per cent of them, but it will get rid of a sizable number of plantar warts that do not respond to other treatments.

I have been careful, naturally, in using it about the face, but I have on a couple of patients been able to get rid of persistent warts of the bearded region by using 2 per cent resin of podophyllum in cold cream. First, I made patch tests to make sure that it did not disagree.

This is an interesting subject. An irritation does not seem to be necessary in order to get rid of the warts. In some persons, as can be seen from the patch test, there is no irritation from resin of podophyllum, and yet the warts disappear.

DR. DUDLEY S. SMITH, Charlottesville, Va.: I should like to confirm Dr. Sullivan's results as far as treating venereal warts is concerned, and I should also like to say that we have had fairly good results from using resin of podophyllum in ordinary flat warts, particularly on the face. These have been treated by applying 20 per cent resin of podophyllum in collodion. This is applied in the office, not given to the patient.

We have also treated several patients with granuloma inguinale with 20 per cent resin of podophyllum in oil along with other routine measures. It causes immediate irritation. The granulating parts of the granuloma inguinale lesions disappear slowly. The applications can be repeated at about ten day intervals.

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hands. Here, too, there was a combination of slightly developed keratoma dissipatum with verruciform lesions on the dorsa of the hands. In 1924, Schönhof<sup>3</sup> described a case of keratodermia maculosa disseminata involving the dorsa. His case was like Hopf's case. Rasch<sup>4</sup> described a patient with disseminated keratosis of the palms, with scattered verruciform lesions on the dorsa of the hands and fingers. In all the others, the volar surfaces were predominantly involved, with only slight involvement of the dorsa. In 1921, Kren<sup>5</sup> reported a case in which apparently only the dorsa of the hands had been involved since childhood. There had apparently been no reaction, and the lesions became stationary.

Hopf concluded that acrokeratosis verruciformis was a reactionless, stationary anomaly of cornification, of nevoid nature, and that this neviform process may be associated with genuine nevi or other nevoid formations. It is histologically important that the substrate in both of Hopf's cases was a circumscribed hyperkeratosis, with enlargement of the stratum granulosum and no parakeratosis, vacuolation or cell degeneration like that usually seen in warts. The lack of reaction of the surrounding tissue and the symmetric distribution persisting unchanged for decades since puberty indicate a structural anomaly of the skin becoming fixed early, most probably to be interpreted as nevoid disease. The finding of familial cases of this condition indicates a genoplasmatic fixation of the cornification anomaly in some cases. Although the eruption usually has its onset at puberty, in some cases it has been present from birth.

In 5 cases of plantar keratosis disseminata, Hopf<sup>6</sup> made a study of the papillary ridges and sweat glands. He was able to demonstrate that the cornification anomaly in these cases had its origin in isolated elements of the papillary ridge system, the initial efflorescence being merely an interruption of the ridge. Once these tiniest foci increased in size, the adjoining portions of ridge were displaced and later involved. The ducts of the sweat glands were involved secondarily, the gland being surrounded by keratosis and thus unable to secrete normally.

In 1930, one month after Hopf's presentation of his first case, Rehn<sup>7</sup> described 4 similar cases in one family, including 1 case of a woman of 28 years whose mother and 2 brothers had similar lesions.

3. Schönhof: Keratodermia maculosa disseminata, *Zentralbl. f. Haut- u. Geschlechtskr.* **15**:407, 1924.

4. Rasch, C.: Keratosis volarum, Adenoma sebaceum, Fibromata dorsi, Eighth Internat. Dermat. Cong., Copenhagen, 1930, case no. 36, p. 1202.

5. Kren: Naeviforme Affektion beider Hände, *Zentralbl. f. Haut- u. Geschlechtskr.* **3**:429, 1921-1922.

6. Hopf, G.: Morphologische und pathogenetische Untersuchungen über primäre Keratosen, *Arch. f. Dermat. u. Syph.* **167**:344-376, 1933.

7. Rehn, cited by Hopf.<sup>6</sup>

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bining with each other, one or another form predominating. Thus characteristic pictures appear according to which predominates. The diffuse disseminated keratoses constitute independent clinical entities. Especially by their combination some common etiologic factor is indicated. From a clinical and morphologic standpoint it would seem logical to classify the various keratoses under nevoid dermatoses.

Darier was the first to draw attention to hyperkeratoses on the hands and feet of patients suffering from follicular dyskeratosis, but he emphasized the fact that the clinical and histologic aspects of these lesions differed from those of Darier's disease, even though he stated the belief that they belonged to the syndrome. In 1891 Boeck described lesions on the dorsa of the hands in Darier's disease, mentioning their similarity to those of *verrucae planae juveniles*. Also lesions of the palms and soles have been described in Darier's disease. Brauer, in his description of *keratoma dissipatum hereditarium*, emphasized the similarity to lesions of the hands and palms described in Darier's disease by French writers.

In 1930, Jadassohn<sup>17</sup> claimed that by careful examination of the palms and soles he could detect forms frustes of Darier's disease even before histologic verification was possible. It had been generally accepted before Hopf's time that anomalies of cornification on the hands and feet in Darier's disease were only part of the general syndrome. Hopf emphasized the fact that these lesions were independent entities appearing in association with Darier's disease or other anomalies of cornification but that there was in all probability some common etiologic factor involved in the various manifestations.

In this connection, it may be of interest to state that great improvement has been noted in some cases of Darier's disease following administration of vitamin A. It is known that a deficient absorption or utilization of vitamin A may be inherited. Also, as regards the varying time of onset of initial lesions, Frazier<sup>18</sup> recently presented a series of cases of vitamin A deficiency, in which the progressive development of follicular hyperkeratosis of the skin was shown to be correlated with the age of the subject. Among infants and children before puberty such lesions occur infrequently, and the younger the child, the milder the degree of follicular damage. The relation of the pathologic changes in the pilosebaceous structures was so correlated with the age of the patient as to suggest that the state of sexual development was the critical factor determining the response of these structures to a deficiency of

17. Jadassohn, J., in discussion on Bettman: Eighth Internat. Dermat. Cong., Copenhagen, 1930, p. 1194.

18. Frazier, C. N.: Hu, C. K., and Chu, F. T.: Variations in the Cutaneous Manifestations of Vitamin A Deficiency from Infancy to Puberty, Arch. Dermat. & Syph. 48:1-14 (July) 1943.

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and plantar keratosis. Transmission is recessive or irregularly dominant. Because the disease was first seen in Meleda, it was believed to be endemic in this island, where consanguinity was exceedingly common. Cases reported from other parts of the world have refuted this theory, however. In this disease, in addition to the eruption on the palms and soles, the lesions may extend in glovelike form over the dorsa of the hands and fingers and frequently also the forearm and leg. The lesions appear at birth or shortly thereafter and progress for about ten years, after which they remain stationary. The nails are involved, frequently also the knees and elbows and not infrequently the lens.

Good results were obtained in 1 case by regional irradiation of the sympathetic nerve fibers (Gouin). The keratosis disappeared two months after application of a dose producing a strong generalized reaction supposed to stimulate the sympathetic system. Some improvement has also been noted following administration of grenz rays and roentgen rays.

In Meleda's disease<sup>22</sup> the histologic changes are confined chiefly to the epidermis. There is decided acanthosis. The rete pegs are plump and of uniform length but four to five times as long as normal. The papillary bodies are small. The stratum corneum is greatly thickened and is the site of the greatest histologic changes. The stratum lucidum is also increased, while the stratum granulosum is thicker over the rete pegs than over the papillary bodies. The sweat glands are usually twice their normal size. There is usually hyperhidrosis and a peculiar odor of rancid butter. It has been suggested that occupational factors may play a part in the more or less severe aspect of the disease.

In epidermodysplasia verruciformis,<sup>23</sup> the epithelial cells appear to be inflated and the nuclei become smaller, seeming to shrink into compact homogeneous masses. The process of vacuolation extends peripherally, thus creating a honeycombed, reticulated effect. Soon the reticular network vanishes, and the cells become truly vacuolated. The intracellular bridges disappear, and there is no evidence of true intracellular or extracellular edema. These changes do not appear in every epidermal cell in sections from typical lesions. Histopathologic changes in typical instances simulate closely those seen in *verrucae planae*, including hyperkeratosis and acanthosis of the epidermis, with a loose basket-weave-like arrangement of the stratum corneum and vacuolation of the prickle cell layer and, in particular, of the stratum granulosum, which

22. Tappeiner, S.: Zur Klinik der idiopathischen diffusen palmoplantaren Keratodermien, Arch. f. Dermat. u. Syph. **175**:453-466, 1937. Niles and Klumpf.<sup>21</sup>

23. (a) Anderson, N. P.: A Case for Diagnosis, Arch. Dermat. & Syph. **30**:731 (Nov.) 1934; **31**:269 (Feb.) 1935. (b) Kogoj, F.: Die Epidermodysplasia verruciformis (Lewandowsky and Lutz), Acta dermat.-venereol. **7**:170-179 (March) 1926. (c) Lenartowicz.<sup>10</sup> (d) Lewandowsky and Lutz.<sup>11</sup>

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condition. The predominant histologic features are a dyskeratosis-like process in the epidermis, with the formation of epidermal vesicles. The eruption occurs in members of the same family and has definite sites of predilection, namely, the neck, axilla and groins. It is suggested that in this process, just as in Dariér's disease, the genetic dystrophy of the basal cells is expressed in a speeding up or a slowing down of the function of the basal cells in their production of prickle cells. No changes could be elicited by even vigorous rubbing of nonpredilected areas.

#### SUMMARY

A review of the world's literature reveals some 25 cases of acrokeratosis verruciformis (Hopf). Among them were cases with a hereditary, familial aspect and others associated with other forms of hereditary and diffuse keratosis. The disease is a region-specific manifestation of a hereditary nevoid dermatosis, with special histologic features distinguishing it from other hereditary keratoses of the diffuse type. Recent investigations suggest that the cause of these lesions lies in some genetic dystrophy of the cells associated with inherited metabolic disturbances, as manifested chiefly in the utilization of vitamin A. Developmental and endocrine influences, as well as acquired or inherited reactivity of local tissue, may explain the manifold and varied manifestations of this dystrophy.

A case of pure acrokeratosis verruciformis (Hopf) is described in detail with histologic changes. The genealogic investigation revealed an involvement of no less than 14 members of the family, covering four generations, thus representing the most extensive genealogic study of this disease condition hitherto reported.

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## GRANULOMA INGUINALE TREATED WITH STREPTOMYCIN

Report of Three Cases

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EVER since 1905, when Donovan<sup>1</sup> described the peculiar intracellular and extracellular encapsulated organisms which he found in fresh spreads taken from ulcerative lesions of granuloma inguinale, the nature of the Donovan body has excited great interest. Though Donovan himself expressed the opinion that the organism is a protozoan, its position in the field of taxonomy was a moot point, eliciting much labor but little light, until Anderson, DeMonbreun and Goodpasture<sup>2</sup> successfully cultivated the Donovan body in the yolk of chick embryos. According to these investigators the organism is a bacillus, for which they proposed the generic name "Donovania" and the specific name "granulomatis."

Under the direction of Herman N. Bundesen, Senior Surgeon (R) U.S.P.H.S. (Inactive), President, Chicago Board of Health.

Dr. Andrew C. Ivy, Professor of Physiology, Northwestern University, assisted and advised in the preparation of this study.

From the Chicago Intensive Treatment Center, Venereal Disease Control Program, Chicago Board of Health in cooperation with the United States Public Health Service.

1. Donovan, C.: Medical Cases from Madras General Hospital, Indian M. Gaz. 40:414, 1905.

2. Anderson, K.; DeMonbreun, W. A., and Goodpasture, E. W.: An Etiologic Consideration of Donovia Granulomatis Cultivated from Granuloma Inguinale (Three Cases) in Embryonic Yolk, J. Exper. Med. 81:25, 1945.

tion in Griesbach's article and in the articles of von Muralt, who had often seen acne confined to the side of the back corresponding to the pulmonary involvement. On investigation I discovered my patient has a chronic fibrotic involvement of the right lung only. Two possible explanations of this apparent connection between pulmonary infection and cutaneous disease have been found. Von Soós,<sup>7</sup> in 1920, reported that in patients with pulmonary or pleural involvement he could demonstrate a peculiar reaction of the skin over the area of dulness. After vigorous rubbing of the skin, especially after a warm bath, the diffuse erythema cleared on the healthy side but persisted as red macules on the diseased side for some time. I find no mention of this phenomenon in later literature, and several attempts to demonstrate it in my patient failed.

Lewith,<sup>8</sup> in 1929, noted persistent cutis anserina and comedos in the zones of hyperesthesia and hyperalgesia in a man with tabes dorsalis. Others have seen fleeting cutis anserina in herpes zoster, gallstone disease, angina pectoris and urethral and gastrointestinal diseases. Lewith described the reflex nervous path and maintained that there is such a basis for some cases of nevus acneiformis, explaining the lesions as due to the increased activity of the sebaceous glands resulting from the irritation of the nerves. I doubt that either of these explains the phenomenon.

My investigation indicated that acne is more often seen among tuberculous patients, and that it persists longer among them than in those who do not suffer from a general infection. This agrees with the commonly seen exacerbation of acne during the course of milder infections. However, in agreement with Griesbach, I observed more instances of acne among convalescent than among very ill patients. Griesbach explained this as an exhaustion of the reticuloendothelial system in the extremely ill patients, such as may cause the tuberculin reaction to become negative. When convalescence has begun, the reticuloendothelial system revives enough to reproduce the reaction in the skin that is called acne.

If it may be assumed that degree of sensitiveness to tuberculin and resistance to tuberculosis are parallel, Loewenthal's<sup>5</sup> recent discovery in regard to the tuberculin reactions in acne may, if substantiated by other investigators, suggest an explanation of the relationship between acne and tuberculosis.

Loewenthal<sup>5</sup> divided his patients with acne and his controls into two groups, persons 26 or younger and persons 27 and older. In the younger

7. von Soós, A.: Ueber eine durch Frottieren erzeugte Hautreaktion bei Lungenkranken, Deutsche med. Wchnschr. 46:13 (Jan. 1) 1920.

8. Lewith, R.: Ueber einen Fall von Cutis anserina persistens und Comedonenacne in Hitzigischer Zone als Beitrag zur Pathogenese der systematisierten Dermatosen, Arch. f. Dermat. u. Syph. 157:153-159, 1929.

The therapy of the disease was ineffective until 1913, when intravenous administration of antimony and potassium tartrate was introduced by de Beaurepaire, Aragão and Vianna.<sup>3</sup> This drug was enthusiastically acclaimed by Low and Newham,<sup>4</sup> Pardo,<sup>5</sup> and Randall, Small and Belk.<sup>6</sup>

Fraser<sup>7</sup> was not impressed with the efficacy of the drug. After a study of 16 patients treated with antimony and potassium tartrate, treatment for 62.5 per cent of whom was regarded as having failed, he stated that the prognosis of granuloma inguinale was poor, and that the results with antimony and potassium tartrate were disappointing.

In 1933 stibophen ("fuadin"—sodium antimony III bis-catechol-2, 4 disulfonate N. N. R.) was introduced by Williamson and his colleagues,<sup>8</sup> who reported on a group of 14 patients, in all of whom cures were obtained.

An excellent recent survey of the effect of antimony preparations, including antimony and potassium tartrate, stibophen and antimony and lithium thiomalate ("anthiomaline"), was reported by Robinson and his colleagues,<sup>9</sup> who found in a study of 46 patients treated with one antimony preparation or another that 60.8 per cent could be cured. For patients failing to respond to antimony they advised surgical measures. They demonstrated the efficacy of excision in 2 patients with small lesions, in whom excision of the affected tissue resulted in cure without the use of any specific chemotherapeutic agent.

Recently the use of resin of Podophyllum has been recommended in the treatment of granuloma inguinale.<sup>10</sup>

In the past four years more than 100 patients have been seen at the Chicago Intensive Treatment Center. Diagnosis of granuloma inguinale in these patients was established not only on clinical grounds but also on the demonstration of Donovan bodies in stained specimens of fresh

3. de Beaurepaire Aragão, H., and Vianna, G.: Pesquisas sobre o granuloma venereo, Mem. do Inst. Oswaldo Cruz. **5**:211, 1913.

4. Low, G. C., and Newham, H. B.: A Case of Ulcerating Granuloma Successfully Treated by Intravenous Injections of Antimony, Brit. M. J. **2**:387, 1916.

5. Pardo, V.: Ulcerating Granuloma of the Pudenda, J. Cut. Dis. **36**:206 (April) 1918.

6. Randall, A.; Small, J. C., and Belk, W. P.: Tropical Inginal Granuloma in Eastern U. S., J. Urol. **5**:539, 1921.

7. Fraser, A. R.: Granuloma Inguinale, Brit. J. Dermat. **37**:14, 1925.

8. Williamson, T. V.; Anderson, J. W.; Kimbrough, R., and Dodson, A. L.: Specific Effect of "Fouadin" (Fuadin) on Granuloma Inguinale: Preliminary Report, J. A. M. A. **100**:1671 (May 27) 1933.

9. Robinson, H. M.; Robinson, H. M., Jr.; Shelley, H. S., and Mays, H. B.: The Treatment of Granuloma Inguinale, South. M. J. **35**:889, 1942.

10. Tomskey, G. C.; Vickery, G. W., and Gatzoff, P. L.: The Successful Treatment of Granuloma Inguinale with Special Reference to the Use of Podophyllin, J. Urol. **48**:401, 1942.

This also is difficult to explain, as is the case of acne confined to one side of the back in the 57 year old man.

The only criticism I would offer is that Dr. Stillians has included in one of his four groups patients with 5 to 20 comedos, which would not seem to be sufficient for diagnosis as acne. The papules and pustules in group 3 or 4 constitute better diagnostic criteria.

This is an interesting problem, and I believe that it deserves further study. I enjoyed hearing the paper.

DR. GEORGE M. MACKEE, New York: I am amazed at the figures that Dr. Stillians has given. I cannot argue against statistics, inasmuch as I have no figures or statistics to offer. However, I spent a period of four years at Saranac Lake, a resort for tuberculous patients, and I was there about one month a year for perhaps ten years after that. During those fourteen years I believe I saw every patient—of whom there were many at Saranac Lake—who had any disease of the skin. Saranac Lake is a large health center. There are twenty or more physicians, none of whom are dermatologists. Consequently, on my yearly trips I would see many patients who had been waiting for me.

Since I quit doing that, I think Dr. Cipollaro has done so. Perhaps he can support what I am about to say.

I saw few cases of acne at Saranac Lake; no more, certainly, than I would see in any other group of persons, perhaps not even as many, and no cases of severe disease. When I went up there, I thought that I would see many cases of acne, severe acne.

DR. ANTHONY C. CIPOLLARO, New York: I would like to confirm what Dr. MacKee has said in relation to this problem. I, like Dr. MacKee, was amazed to find that acne vulgaris is so prevalent among persons with tuberculosis.

DR. A. W. STILLIANS, Chicago: On the question of 5 to 20 comedos, I took into consideration the fact that the condition of these patients varied, the acne varied from time to time, and a patient who has 5 to 20 comedos at one time may have an increased eruption during the menstrual period. The judgment as to whether acne is present or not, or of its degree, is difficult because of this almost daily variation in its intensity. I chose the reports of Hinrichsen and Ivy because they were made in my section of the country, and I based my comparison on them because I believe that acne varies in different climates.

spreads. Almost all of these patients were treated with antimony and potassium tartrate, stibophen or antimony and lithium thiomalate. It is not our purpose to give a detailed report of the results obtained in these patients, since our experience closely paralleled that of Robinson and his colleagues.<sup>9</sup> We are in complete agreement with Brandt and Gatewood,<sup>11</sup> who stated, "The effect of antimony preparations . . . is pronounced in the early phases of the disease and decreases in direct ratio to its duration."

With the recent demonstration of the bacillary nature of the Donovan body it was felt that a study of the effect of an antibiotic on the disease was warranted. Inasmuch as adverse reports on treatment with penicillin had been published,<sup>12</sup> it was decided to limit this study to the effect of streptomycin on granuloma inguinale.

Accordingly, 3 patients were selected, who presented clinical evidence of granuloma inguinale and who had not received any specific therapy for the disease prior to entering the Center. Freedom from syphilis, chancroid and lymphogranuloma venereum was established, so far as dark field examination, serologic tests, cutaneous tests and clinical examinations were concerned. In all 3 patients Donovan bodies were demonstrated prior to the initiation of therapy. Their case histories are presented here.

#### REPORT OF CASES

CASE 1.—M. N., a Negro woman aged 26, was admitted to the hospital on Feb. 18, 1946. She stated that for the preceding fifteen months she had suffered from a "sore on the privates" which had slowly increased in size until the entire genital area was involved. She gave a vague history of having received treatment for "gonorrhea" twelve months previous to admission. Treatment had consisted of fifteen intravenous and thirty intramuscular injections of drugs, with whose nature she was not familiar. She had noted no improvement of her genital condition while receiving this therapy.

Examination revealed a well nourished, well developed Negro woman, whose disease process was localized exclusively in the external genitalia. Chronic woody lymphedema had produced an enlargement of both labia majora to approximately twice their normal size. Along the medial portions of these labia, extending their full length, was an ulceration characterized by a continuous nodular serpiginous border. The ulceration extended medially to invade both labia minora, the fourchet and the clitoris. The vagina and the cervix were not involved, and the perianal region was likewise free of disease. The inguinal regions were completely spared, nor was there any inguinal lymphadenitis.

The base of the ulcer was clean and presented a velvety exuberant bright red appearance particularly discernible on the labia minora.

Repeated examination of serum from the ulcer by means of the dark field microscope did not reveal *Treponema pallidum*. The reaction to the serologic test for syphilis (Kahn) was negative. The reaction to the Frei test was reported as

11. Brandt, R., and Gatewood, T. S.: Early Diagnosis of Granuloma Inguinale, Am. J. Syph., Gonor. & Ven. Dis. **25**:48, 1941.

12. Haserick, J. R.: The Failure of Penicillin in the Treatment of Granuloma Inguinale, Arch. Dermat. & Syph. **52**:182 (Sept.) 1945.

chief complaints, and there was a high incidence of cutaneous lesions of the specific and the nonspecific type or both. Death occurred on the average of one and nine-tenths months after the patient's initial visit to the clinic or eight and four-tenths months after the appearance of the initial symptom.

#### HEMATOLOGY

Reschad and Schilling-Torgau<sup>1</sup> in 1913 were the first to differentiate monocytic leukemia from the myelogenous and lymphatic types. They stated the belief that the monocyte originated in the reticuloendothelial system. In 1923 Naegeli<sup>2</sup> proposed that monocytes were derivatives of myeloblasts and hence that monocytic leukemia was a variant of myelogenous leukemia. Conflicting views concerning the origin of the monocyte as well as observation of cases of leukemia in which at some time smears of the blood showed a high percentage of monoblasts, monocytes and cells of the myeloid series led to the subdivision of monocytic leukemia into the Schilling and Naegeli types. This classification of monocytic leukemia is still accepted by some authors, although the rapid advances in hematology seem to indicate that this view is no longer tenable. Downey,<sup>3</sup> Bell<sup>4</sup> and Montgomery and Watkins<sup>5</sup> considered the Naegeli type as a variant of myelogenous leukemia. Sterne<sup>6</sup> expressed the opinion that the Naegeli type usually terminates in myelogenous leukemia or reverts to it at some time during the course and that a temporary monocytic predominance may be encountered during the course of myelogenous leukemia. Doan and Wiseman<sup>7</sup> stated that the monocyte in the blood is identical with the monocyte in the tissues and is a derivative of the mesenchymal reticular tissue. They further stated that myelocytes and young lymphocytes occur frequently in the blood stream of patients with monocytic leukemia but that monocytes are

1. Reschad, H., and Schilling-Torgau, V.: Ueber eine neue Leukämie durch echte Uebergangsformen (Splenozytenleukämie) und ihre Bedeutung für die Selbständigkeit dieser Zellen, München. med. Wochenschr. **60**:1981-1984, 1913.
2. Naegeli, O.: Blutkrankheiten und Blutdiagnostik, Berlin, Julius Springer, 1923.
3. Downey, H.: Diseases of the Blood, in Bell, E. T.: A Text-Book of Pathology, ed. 2, Philadelphia, Lea & Febiger, 1934.
4. Bell, E. T.: Text-Book of Pathology, Philadelphia, Lea & Febiger, 1944, p. 423.
5. Montgomery, H., and Watkins, C. H.: Exfoliative Dermatitis as a Manifestation of Monocytic Leukemia (Schilling), Minnesota Med. **21**:636-641 (Sept.) 1938.
6. Sterne, E. H., Jr.: Diagnosis of Monocytic Leucemia from Examination of Peripheral Blood Stained with Wright's, with Report of Five Cases, Ohio State M. J. **38**:234-238 (March) 1942.
7. Doan, C. A., and Wiseman, B. K.: Monocyte, Monocytosis and Monocytic Leukosis: Clinical and Pathological Study, Ann. Int. Med. **8**:383-416 (Oct.) 1934.

By the ninth day of treatment the ulcer had shrunk to half its initial size, and the border was no longer conspicuous. On April 2 the lesion was completely epithelized with the exception of one erosion of 5 mm. at the posterior commissure.

Additional streptomycin could not be given because of the exhaustion of our supply. The patient was instructed to return to the hospital for observation, and other therapy was not instituted. On April 16 the lesion had increased in size to approximately 1 cm., and from that time until June 17 there was no change in the appearance or in the size of the lesion.

Ten days after streptomycin was initially administered it was no longer possible to demonstrate Donovan bodies from scrapings of tissue taken from the fourchet.

#### COMMENT

It is admitted that the daily doses of streptomycin administered to these patients were small. Our supply of streptomycin was, however, limited, and in view of our experience with other antibiotics in the treatment of syphilis it was deemed wiser to protract the treatment period, using small doses, than to expend all of the drug over a short period of time. It is possible that more spectacular results might be achieved using larger amounts of streptomycin.

#### CONCLUSION

Three patients presenting unequivocal clinical and laboratory evidence of granuloma inguinale were treated with streptomycin. All 3 patients showed excellent clinical improvement with disappearance of Donovan bodies from the lesion. Two of the 3 patients exhibited relapse after the supply of streptomycin was exhausted.

One patient treated with streptomycin for forty-one days was observed for two and one-half months after the completion of therapy with no evidence of relapse.

It is believed that streptomycin is a valuable drug in the treatment of granuloma inguinale.

1200 Main Street.

## HISTOPATHOLOGY

It is often difficult to differentiate monocytic leukemia histologically from the other members of the lymphoblastoma group. The various types of primitive blood cells are not easily recognized, because of changes that take place in the preparation of the slides. There are, however, some fairly constant features that are helpful in making a diagnosis. The epidermis is usually not involved if ulceration does not occur. A narrow band of normal corium separating the epidermis from the tumor tissue may be present. There is an increase in reticulum. The cellular infiltrate is invasive and consists of large nodules composed of closely packed cells, often located around a dermal appendage or blood vessel. Loveman<sup>9</sup> has pointed out that the infiltrate extends between the strands of connective tissue without destroying them as in other leukemias. The cytoplasm of the invading cells is usually slightly basophilic and vacuolated and varies considerably in amount and density. The nuclei are large, often indented or kidney shaped and have well defined, strongly basophilic nuclear membranes and clear, basophilic or neutrophilic pale-staining nucleoplasm. One or two large basophilic nucleoli are present in the nucleus. Montgomery and Watkins<sup>5</sup> stated that the characteristic feature is the longitudinal grooving of the nuclei. This consists of a narrow band or fold of chromatin extending diagonally or longitudinally across the nucleus. This is not always distinguishable, but when seen it is extremely helpful. Mitoses are present in moderate numbers. A general pathologist will often make a diagnosis of some form of sarcoma in these sections. This occurred in several of our cases. Mycosis fungoides may also simulate monocytic leukemia histologically, particularly in the early stages.

## CUTANEOUS MANIFESTATIONS

Osgood<sup>10</sup> reviewed 127 cases of monocytic leukemia and reported 6 additional cases in 1937. He gave tables with percentages showing the incidence of various hematologic and clinical manifestations. He divided the patients with cutaneous manifestations other than petechiae into two groups: group I, having nodules in the skin which are firm and painless and, on histologic examination, are composed largely of monocytes and their progenitors (this type seemed to be specific for monocytic leukemia), and group II, having staphylococcal infection of the skin (boils and carbuncles). Of the 133 cases reported to 1937 he found 12 cases with specific lesions of the skin and 3 with staphylococcal infection of the skin. Eighty per cent of 88 patients examined for

9. Loveman, A. B.: Monocytic Leukemia Cutis: Report of Case with Biopsy Studies, *South. M. J.* 29:357-364 (April) 1936.

10. Osgood, E. E.: Monocytic Leukemia: Report of Six Cases and Review of One Hundred and Twenty-Seven Cases, *Arch. Int. Med.* 59:931-951 (June) 1937.

## TREATMENT OF UNDERMINING ACNE LESIONS BY EXTERIORIZATION

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AND

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**A**CNE vulgaris in patients who have served in the tropics in the interval between 1942 and 1945 has occasionally presented complications consisting of chronic undermining sinuses or undermined bases in the acne zone. Treatment has been difficult as far as permanent cure is concerned. Men who arrived in the South Pacific with acne lesions already present usually noticed aggravation of the lesions within a few months. Many other men who had never before experienced acne had lesions on the face, neck, chest, back, arms and buttocks shortly after arriving in the South Pacific. The increased incidence of acne lesions in American troops in the tropics may possibly be explained by the greater heat and humidity and the resulting increased perspiration, a good medium for bacterial growth. Other factors possibly responsible may have been dietary deficiencies, lowered general resistance, hypersecretion of the sebaceous glands due to the increased heat and the intake of quinacrine hydrochloride. Endocrine activity in relation to tropical acne has not been fully reported on as yet. Whether the lesions are related to a symbiosis of organisms or may be considered minor clinical manifestations of the chronic indolent ulcers described by Meleney is unknown. They do not present areas of spreading gangrene, and the areas of local necrosis do not spread too widely.

A careful perusal of the literature of the past ten years revealed little on tropical acne. Stitt<sup>1</sup> did not consider it at all. Ambler<sup>2</sup> merely mentioned cystic acne in the South Pacific. Duemling<sup>3</sup> recently gave a good description of the problems of the treatment of tropical acne and reported the use of the exteriorization operation in deep cystic tropical acne.

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From the Department of Dermatology, University of Maryland School of Medicine, Baltimore.

1. Strong, R. P.: Stitt's Diagnosis and Prevention of Tropical Diseases, ed. 6, Philadelphia, The Blakiston Company, 1942.

2. Ambler, J. V.: Experience of a Dermatologist in the Southern Pacific, Arch. Dermat. & Syph. 49:224 (March) 1944.

3. Duemling, W. W.: Cutaneous Diseases in the South Pacific, Arch. Dermat. & Syph. 52:75 (Aug.) 1945.

patient. The color varied from light pink to violescent, with a tendency for the older lesions to become darker and deeper violescent. Nodules which had apparently undergone partial involution were brown and covered with fine sparse scale. Mercer<sup>14</sup> and Freeman<sup>15</sup> described a pale, shotty, papular eruption which was deep in the corium and was more easily felt than seen. None of our patients manifested this type of eruption. Furunculosis was encountered three times. It was the initial complaint in 3 of our patients and in 1 of Osgood's. Montgomery stated that it was a late manifestation in his series. Large indurated ulcers were present in 3 of our cases. The section of tissue from the margins of the ulcers showed in addition to an acute inflammatory reaction a monocytic infiltration identical with that present in nonulcerated lesions. The individual ulcers were formed by necrosis of large nodules, leaving large, deep crateriform ulcerations with infiltrated undermined margins. Jaundice was present in 2 patients. Purpura was a common manifestation, occurring in 25 per cent of the series. In some of these cases specific lesions were also present. Evans<sup>12</sup> stated that purpura is exceedingly common in monocytic leukemia and that the spleen and liver are seldom enlarged clinically, but moderate enlargement of both is frequently observed at postmortem examination. This also has been our experience.

Only 12 of our patients had palpably enlarged spleens. Four of these were especially large, extending to the umbilicus. Twelve patients had enlarged lymph glands, but in only a few was adenopathy striking.

Weakness was by far the commonest initial symptom (25 per cent) in our series of cases. Sore throat and infection of the upper respiratory tract were also frequent early symptoms. In several patients poor healing after tonsillectomy or extraction of teeth was the first intimation of the disease. The chief complaints on patients' admission to the clinic were weakness, anemia, fever, stomatitis, hemorrhages of the mucous membrane and sore throat. By this time the cutaneous lesions, which were usually asymptomatic, were no longer of primary concern to the patient.

#### TREATMENT

Sterne<sup>6</sup> pointed out that treatment of acute conditions with roentgen rays may be catastrophic. An unfavorable reaction to roentgen ray therapy was observed in 1 of our cases (case 8). A few patients were treated with deep roentgen therapy, but results were poor and consequently we have abandoned this therapy. Superficial roentgen therapy caused temporary improvement in the cutaneous lesions in 3 of our cases. Montgomery and Watkins<sup>16</sup> also used roentgen rays to

16. Montgomery, H., and Watkins, C. H.: Exfoliative Dermatitis as a Manifestation of Monocytic Leukemia (Schilling), Proc. Staff Meet., Mayo Clin. 13:294-297 (May 11) 1938; footnote 5.

Tropical acne in American troops in the South Pacific consisted of essentially the same comedos, erythematous papules, cystic lesions and scars as in acne vulgaris of patients in the United States. In the former, however, the lesions were more profuse, larger and more severe in character. The sites usually involved were the face, back, chest, back of the neck, arms and buttocks. In addition to these ordinary lesions of acne a somewhat different type of lesion was observed in some cases of tropical acne. These unusual lesions were large, deep and cystic in some cases and in others were deep-seated areas of cellulitis, or abscess formation, extending down to and including the subcutaneous tissue. It is these unusual types of lesions with which this paper is concerned. These deep-



Fig. 1.—Severe deep multiple undermined cystic lesions with numerous sinus openings.

seated cystic or abscess-like lesions were extremely painful and indolent, and often were elevated above the surface of the skin, with adjacent induration of the skin as well as erythema. The lesions were commonly associated with a severe keloidal type of scarring, and the hypertrophic scars, frequently linear in character, had multiple sinus openings with persistent drainage. Sometimes the scars were atrophic. Undermining was almost always present, the lesions extending peripherally beneath the surface of the skin for a considerable distance in the form of pockets and sinus tracts with purulent drainage from single or multiple orifices. These lesions did not respond to ordinary methods of treatment for acne but continued to spread, new sinuses making their appearance and draining purulent material, while old sinus openings temporarily healed. These unusual lesions were found almost invariably on the back of the

can do to relieve the oral lesions is appreciated by the patient. A dentist called in consultation in our case took care of the oral treatment of the disease. He cut away the sloughs and applied local antiseptic medication. I believe that the use of penicillin troches might be of some value in taking care of this secondary infection with Vincent's organisms, which becomes dominant in the terminal stages of the disease. I believe a bone marrow puncture with the demonstration of almost pure cultures of monocytes represents the most conclusive diagnostic procedure early in the disease.

DR. W. R. HUBLER, Youngstown, Ohio: I thank Dr. Arnold and Dr. Winer for their discussion. I had not thought of the resemblance to leprosy.

In answer to Dr. McCarthy's questions, Doan and Wiseman in a recent paper concluded that monocytic leukemia constituted 16 per cent of all leukemias. Rosenthal and Harris felt that the incidence of leukemias paralleled the types of cells in the blood and gave 5.9 per cent as the incidence of monocytic leukemia.

Curiously enough, we were unable to find Vincent organisms in most of the patients that had serious oral infections. Streptococci and staphylococci were commonly found.

I agree with Dr. McCarthy that penicillin should be tried for the relief of oral symptoms. However, we have not had a patient with severe oral lesions since penicillin has become freely available.

neck, but sometimes on the buttocks, face or back. Why the back of the neck was most often affected is unknown. Cystic acne with slight undermining, less severe than the tropical cystic lesions, is observed occasionally in the United States. The ordinary papules, pustules and comedos of tropical acne, once the patient is evacuated to the United States, have been found to respond well to routine acne therapy: manual expression of comedos, repeated incision and drainage of large pustules, daily application of a sulfur lotion, warm compresses several times a day to indurated lesions, low carbohydrate diets, daily ultraviolet radiation in gradually increased doses for patients with superficial lesions and 100 to 150 roentgens of unfiltered radiation weekly for four weeks for



Fig. 2.—Same case as in figure 1 immediately following exteriorization. Note extent and depth of undermining.

patients with deeper lesions. Penicillin injected every three hours intramuscularly, in five daily doses of 20,000 units, for a period of one to three weeks proved to be of no value in ordinary tropical acne or in deep cystic undermining acne lesions in the many cases in which we employed it during a twenty month period. Perhaps the reason that penicillin did not help tropical acne was that the organisms were walled off and inaccessible to penicillin even though the organisms present may be, and often are, sensitive to the drug.

The severe deep cystic undermining acne lesions did not respond to ordinary therapy, even when administered for three to six months. Surgical intervention was necessary, and the lesions were exteriorized. Duemling<sup>3</sup> mentioned this method of therapy in such cases and claimed good results with this type of operation. Prior to reading Duemling's article, we had independently, for six months, employed this operation

ment of Gas Casualties of the National Research Council; (2) Cornell University Medical College (project OEMcmr 103); (3) Hospital of the University of Pennsylvania (project OEMcmr 24); (4) Medical Department, Chemical Warfare Service, United States Army; (5) Naval Research Laboratory, Anacostia, Md.; (6) United States Food and Drug Administration, Washington, D. C.; (7) Wilmer Institute, Johns Hopkins University Hospital (project OEMcmr 9); (8) Arthur D. Little, Inc., Boston; (9) Bristol Myers Co., Hillside, N. J.; (10) E. I. duPont de Nemours & Co., Wilmington, Del., and, (11) Norwich Pharmacal Co., Norwich, N. Y.

This subcommittee's pharmaceutical and chemical program for the development of stable BAL preparations has been discussed in detail by Lazier.<sup>3</sup> Moreover, the biologic evaluation of the therapeutic and decontaminating efficacy of the various preparations on rabbits' eyes has been the subject of previous reports.<sup>4</sup>

The present communication will therefore deal solely with the biologic evaluation of BAL preparations in regard to their relative decontaminating, therapeutic and protective efficacy when used on the animal and human skin. The formulas discussed in the present report, as well as the results of the biologic evaluations, were largely an outcome of the cooperative effort of the aforementioned groups. Many of the methods for biologic evaluation had been developed by us; however, in development of these methods a great deal of help was derived from other investigators, including some independent workers not included in the official cooperative program.

In setting up the program it was decided that the biologic evaluation of vehicles for cutaneous application of any active agent should include the following tests:<sup>5</sup> (1) tests for efficacy in achieving the purposes for which the preparation was primarily intended, including tests of samples before and after artificial or "natural" aging procedures; (2) tests for irritancy on human skin; (3) tests for sensitizing capacity on human skin; (4) tests for systemic toxicity on cutaneous application, and (5) tests for acceptability to the intended user.

Certain of these tests in the biologic evaluation of BAL preparations, such as percutaneous toxicity tests<sup>6</sup> and tests for sensitization have been discussed elsewhere.<sup>7</sup>

3. Lazier, W. A.; 1943. Incomplete references in this paper are to reports which were secret, confidential or restricted at the time of presentation.

4. (a) Adler, F. H., and Leopold, I. H., 1943. (b) Friedenwald, J. S., and Hughes, W. F., 1943. (c) McLean, J. M., and Cuthbert, M., 1943.

5. Sulzberger, M. B.; Baer, R. L.; Kanof, A., and Lowenberg, C.: Methods for the Rapid Evaluation of the Beneficial and Harmful Effects of Agents Applied to the Human Skin, *J. Invest. Dermat.* 7:227-238 (Oct.) 1946.

with success in treating patients with the severe deep cystic undermining types of acne discussed in this report.

Exteriorization (marsupialization) is a term that may properly be applied to the surgical treatment of deep undermined cystic or abscess-like acne. By exteriorization is meant opening up an undermining acne lesion completely and exposing its base, thus allowing healing from within. The pathologic structure of undermining acne lesions reveals an indolent area of cellulitis, with or without superficial abscesses and with a variable degree of undermining. This area extends as a smooth basal layer lined with an avascular granulation tissue or may present a basal layer of epithelium in the hypertrophic lesion where the acne



Fig. 3.—Same case as in figures 1 and 2, eight weeks following exteriorization. Note atrophic residual scars.

process is raised above the true skin. Characteristically, the abscess pocket drains through a superficial sinus that extends into either the abscess cavity or the undermined area. Exudate from either the abscess or the undermined area varies from a thin serous to a frank purulent one. Preparation of the local skin area consists of washing with white soap and water, shaving all cutaneous hair, cleansing the skin with several applications of ether, with 70 per cent alcohol as a second wash, and final preparation with an antiseptic such as merthiolate or "zephiran." A mosquito hemostat can be introduced into the sinus and a general idea of the extent of undermining obtained. The loop scalpel of an electro-surgical unit is an adequate instrument for exteriorization. All of the acneform area is excised. This is accomplished by making an initial

necrosis, often surrounded by a rather wide zone of diffuse or reticulated superficial hemorrhage and inflammatory erythema (fig. 1). In addition there is usually considerable surrounding and underlying edema, often reaching large proportions. The edematous areas frequently appear as tumors which are jelly-like in consistency and cool to the touch.

Within the next few days the edema gradually subsides and the hemorrhages begin to pale, leaving a diffuse, yellowish discoloration of the skin and underlying tissue. This discoloration is probably due to diffusion and degradation of blood pigments. When large areas of hemorrhage have been present the entire skin of the animal may assume

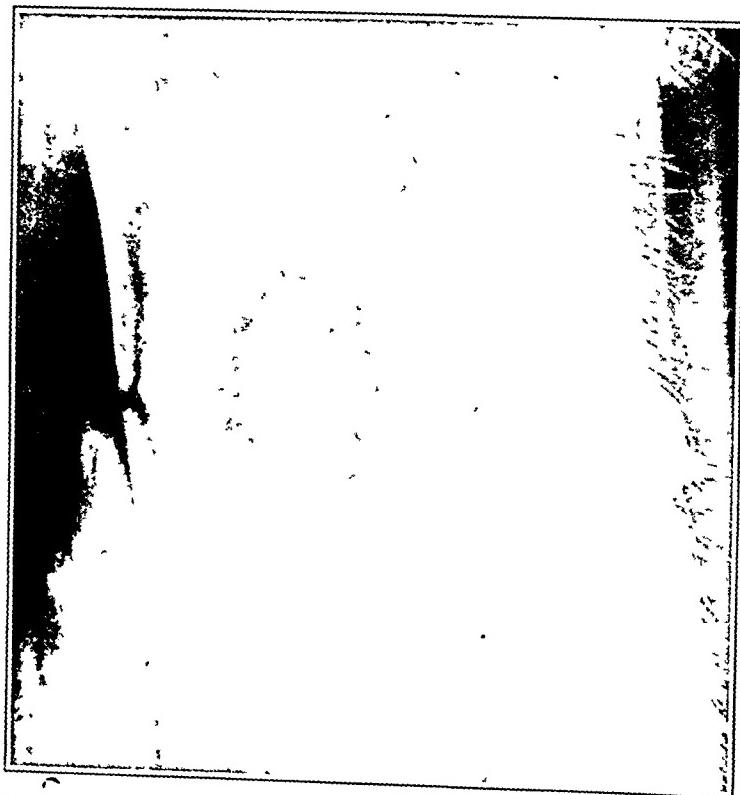


Fig. 1.—Untreated lesion twenty-four hours after application of approximately 1.6 mg. of liquid lewisite to a rabbit's belly. Note the central white necrosis and surrounding hemorrhage and edema.

an icteric tinge. As the edema subsides a hard, indurated margin forms immediately around the crust or ulcer. Within about a week the necrotic zone becomes transformed into an adherent brownish or purplish black crust or eschar. This crust, when removed, intentionally or accidentally, shows a subjacent ulcer. The damage from relatively large doses of liquid lewisite, such as 2 mg. or more, may penetrate deeply into the muscles and even to and into the viscera beneath. The ulcerated zone or the area under the crust becomes gradually more shallow and heals slowly from the periphery; the crust becomes dry, lifting or peeling off at the edges as healing advances. Healing with scar formation is usually complete in about five to seven weeks.

incision through the acneform area down to the undermined base. The periphery is identified and the overlying thickened skin over the central portion of the area removed. A base of granulation tissue is excised. If epithelium presents itself as the base, it is not excised. Bleeding points are few and when encountered are lightly coagulated. The periphery of the undermined area is carefully examined and gently palpated to be sure that there is no minute sinus tract extending into the superficial subcutaneous tissue, since all outward sinuses must be opened. It is best to bevel the periphery of the excised area, as this accelerates healing. The wound is dressed with a petrolatum strip and a gentle pressure gauze dressing. The next dressing is done five to seven days later, and either dilute solution of sodium hypochlorite or isotonic solution of sodium chloride is used for two to three weeks while a clean

*Summary of Eight Cases in Which Treatment Was by Exteriorization*

Case No.	Location of Lesions	Tropical Origin	Tropical Aggravation of Pre-existing Acne	Duration of Undermined Lesions with Ordinary Therapy	Bacterial Organisms	Result after Exteriorization
1	Neck	No	Yes	8 mo.	Staph. albus	Healed in 9 weeks
2	Neck	No	No	6 mo.	Staph. albus	Healed in 11 weeks
3	Neck	No	Yes	4 yr.	Hemolytic Str. and staphylococcus	Healed in 4 weeks
4	Face and neck	No	Yes	6 mo.	Staph. aureus	Healed in 8 weeks
5	Back	Yes	No	12 mo.	No cultures	Healed in 10 weeks
6	Buttocks	No	Yes	4 mo.	Hemolytic Str. and staphylococcus	Healed in 6 weeks
7	Neck	No	Yes	6 mo.	Staph. albus	Healed in 9 weeks
8	Neck	No	Yes	3 mo.	Hemolytic Str.	Healed in 10 weeks

granulating surface develops at the base and a thin layer of fibrin and epithelium comes in from the periphery. In 1 patient with cervical acne the wound became excruciatingly painful about five days after exteriorization. This was promptly relieved with a cod liver oil ointment while compresses of isotonic solution of sodium chloride and Peruvian balsam made the pain worse. The question was raised whether this was a phase of synergistic bacterial gangrene, but culture determinations showed only a nonhemolytic staphylococcus. The ultimate fate of the healed wound is unknown at the time of writing, except that residual atrophic and hypertrophic large scars appear. Visible extensive facial and posterior cervical scars may require later excision and grafting. The present status of wound healing suggests that the apparently extensive undermined lesions heal with innocuous cicatrices that do not tend to break down. The ultimate fate of the cicatrices should be reported on later. The table summarizes 8 cases in which treatment was by exteriorization.

thereafter. Some investigators<sup>8</sup> prefer to make readings up to definitive healing with scar formation. We have found that readings at seventy-two hours and at one week are sufficient to give a reliable index of severity and extent of damage—and thus, conversely, of comparative efficacy of the different BAL preparations used.

While many refinements were tried, it was found that clinical evaluation, clinical descriptions of the various forms or zones of damage, together with photographic records as required, in their aggregate constitute a method which has the advantages of simplicity and speed and is for the purposes of these tests sufficiently precise for evaluating significant differences in degree of lewisite damage.

*Effect of 5 Per Cent BAL Preparations on Lewisite Lesions in Rabbits.*—With the exception of one of the earliest American reports, all investigators agree that the local application of BAL or preparations containing BAL exerts a strikingly beneficial action in counteracting or inhibiting the effects produced by liquid lewisite on the skin. This action is in all likelihood due to a combination of decontaminating and specific therapeutic effects.<sup>9</sup>

Comparisons of the BAL-treated sites with the lesions seen at the untreated control sites showed that BAL reduced all phases and types of damage when it was applied to rabbits' skin contaminated by approximately 2 mg. of liquid lewisite. The shorter the interval between application of vesicant and application of BAL, the greater the benefit. When the applications were made as early as one to thirty minutes after contamination, there was a material reduction of local damage. Sometimes only a small central crust developed. Applications of BAL made after forty-five to sixty minutes and even up to six hours<sup>10</sup> still reduced the depth, size and extent of necrosis, ulceration, edema and hemorrhage but did not prevent these changes.

TESTS ON PROTECTION.<sup>11</sup>—The studies on protection are carried out by reversing the procedure previously described under "Treatment and Decontamination," i. e., by first applying measured amounts of BAL preparations to marked, symmetrically placed, equal areas on the depilated rabbit's belly, and then applying measured amounts of liquid lewisite at different, precisely measured periods after the application of BAL.

8. (a) Calvery, H. O., 1943. (b) Salter, W. T.; Bass, T. H.; Bullock, J. B., and Fishman, J. B., 1942.

9. "Decontamination," as used here, denotes the use of agents for removal and/or inactivation of vesicant already present on the test subject. "Specific treatment" as used here denotes the use of agents which counteract or inhibit the damaging effects of the vesicant which has already penetrated into the tissues.

10. Calvery, H. O., 1943.

11. "Protection" as used here describes the beneficial effects of any measure used before the exposure of the skin to the vesicant agent.

### HISTOPATHOLOGY

In 2 cases in which exteriorization was performed material was submitted to the pathologist. Microscopic examination disclosed the following facts in one of the cases: "There were irregular hypertrophy and distortion of stratified squamous epithelium with spongiosis and a few small foci of degeneration. Some parakeratosis and hyperkeratosis were seen. A few spots showed ulceration of epithelium and a superficial chronic inflammatory exudate with amorphous debris. In the involved area the subcutaneous tissue showed considerable edema and an acute purulent process some of which was seen extruding through a break in the epithelium. In the remainder of the corium where the tissue was generally normal there were some scattered foci of inflammatory cells some of which were perivascular. In the region of epithelial hypertrophy there was also a deep depression which contained much eosinophilic debris, some blood and inflammatory cells. This area represented a degenerated distorted comedo." In the second case the following was reported: "Intensive diffuse and focal chronic inflammatory reaction with considerable vascular congestion was seen. Some fibrous tissue was present. Diagnosis was subacute and chronic cellulitis, moderately severe." Thus, the pathologic picture was one of deep-seated subacute and chronic inflammation.

### SUMMARY

In cases of tropical acne both ordinary lesions and deep undermined cystic, or abscess-like, lesions are frequently seen. The latter tend to form on the buttocks and the back of the neck where they spread beneath the surface of the skin, forming pockets and sinus tracts and atrophic and hypertrophic scars with constant purulent drainage and concomitant subjective discomfort for the patient. These lesions are occasionally seen in nontropical acne. The predominant organisms found in these lesions are aerobic and anaerobic staphylococci and streptococci (hemolytic). Penicillin is of no value in these cases. Ordinary acne lesions respond to present standard therapy, but the deep cystic undermined lesions are resistant to all such methods even if tried for six or more months. Exteriorization with the cutting current in 8 cases gave uniformly good results in the deep cystic undermined, or abscess-like, lesions, and healing, with only residual hypertrophic or atrophic scars, occurred in six to twelve weeks. As time has elapsed and the scars of exteriorized zones have become more mature, it is apparent that the bulk of the healed areas will not require grafting for cosmetic reasons.

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Grass Valley, Calif. (Dr. Benteen).

## Clinical Notes

### FAILURE OF RESIN OF PODOPHYLLUM IN THE TREATMENT OF VERRUCA VULGARIS

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AND  
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With the introduction of the use of resin of podophyllum in the treatment of condyloma acuminatum by Kaplan,<sup>1</sup> it was natural that attempts were made to use this agent in the treatment of verruca vulgaris and verruca plana. Culp and Kaplan<sup>2</sup> stated that 25 per cent resin of podophyllum in liquid petrolatum was of no value in the treatment of "typical horny verrucae." With the exception of 1 instance of multiple warts of the face, which was treated by MacGregor<sup>3</sup> with 25 per cent resin of podophyllum in liquid petrolatum, there are no reports of any consistent success with this agent in the treatment of verruca vulgaris or verruca plana situated on the glabrous skin.

Because it was considered possible that the failure of this method of treating warts was due to the lack of penetration of the resin of podophyllum through the thick horny surface when applied in the usual vehicles, resin of podophyllum was incorporated in the penetrant material introduced by MacKee, Sulzberger, Herrmann and Baer.<sup>4</sup> The formula used consisted of 20 Gm. of resin of podophyllum added to 100 cc. of a penetrant base. The latter contained two parts by weight of sodium alkyl benzene sulfonate mixture, two parts by weight of antipyrine, five parts by volume of propylene glycol and two parts by volume of water.

Fifteen unselected patients with verruca vulgaris on the hands, the dorsa of the feet or the face were treated with the following methods: (1) simple topical application without massage, (2) topical application massaged in with a glass rod, (3) application with massage after thorough maceration with a 40 per cent salicylic acid plaster, (4) application with massage after the cornified surface was pared off until the capillaries were exposed and (5) topical application covered by collodion.

The patients were examined over a period of one to three months. With 1 exception, a periungual wart, the warts did not respond to the treatment. The disappearance of the wart in 1 of the 15 patients could be considered an instance of spontaneous disappearance or disappearance following suggestion therapy (Sulzberger and Wolf<sup>5</sup>).

From the Skin and Cancer Unit, New York Post-Graduate Medical School and Hospital, Columbia University.

1. Kaplan, I. W.: Condylomata Acuminata, New Orleans M. & S. J. **94**:388 (Feb.) 1942.
2. Culp, O. S., and Kaplan, I. W.: Condylomata Acuminata: Two Hundred Cases Treated with Podophyllin, Ann. Surg. **120**:251 (Aug.) 1944.
3. MacGregor, J. V.: Treatment of Soft Warts with Podophyllin, Brit. M. J. **1**:593 (April 28) 1945.
4. MacKee, G. M.; Sulzberger, M. B.; Herrmann, F., and Baer, R. L.: Histologic Studies on Percutaneous Penetration with Special Reference to the Effect of Vehicles, J. Invest. Dermat. **6**:43 (Feb.) 1945.

(Footnotes continued on next page)

## ATYPICAL LICHENOID DERMATITIS

A Drug Eruption Due to Quinacrine Hydrochloride (Atabrine)

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AND

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IMMEDIATELY following the Buna campaign in New Guinea in 1943 a new cutaneous syndrome was repeatedly observed among the Australian and American soldiers returning to the base hospitals in Australia. The eruption puzzled many experienced dermatologists, and it was not until the same clinical picture was repeated in increasing numbers that a few medical officers realized that they were dealing with a new disease, hitherto undescribed. The uncertainty of diagnosis is witnessed by the wide variety of names attached to the disease, such as "tropical lichen planus," "atypical lichen planus," "quinacrine hydrochloride dermatitis," "lichenoid dermatitis," "atypical lichenoid dermatitis" and, among the G. I.'s, simply "New Guinea Rot." Since it appeared that the eruption was associated with the enforced ingestion of quinacrine hydrochloride (atabrine) in a malarial suppressive routine, discussion of the disease became officially top secret. The result was that information about the cutaneous disease was disseminated by word of mouth among medical officers, and its clinical characteristics became jumbled and, to say the least, vague. A large number of patients with all types of diseases of the skin were therefore returned to the United States as having "quinacrine hydrochloride dermatitis." While reports were submitted to the Medical Department of the United States Army in June 1944 by Schmitt<sup>1</sup> and an exhaustive study of 200 cases was reported by Ambler<sup>2</sup> in December 1944 and later by Novy<sup>3</sup> and others

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Read at the Sixty-Sixth Annual Meeting of the American Dermatological Association, Hot Springs, Va., June 10, 1946.

Material in this article was made available through the cooperation of Admiral J. C. Owen (MC), U. S. N., and the medical personnel of the Seventh Fleet.

1. Schmitt, C. L.; Alpins, O., and Chambers, G.: Clinical Investigation of a New Cutaneous Syndrome, Arch. Dermat. & Syph. 52:226 (Oct.) 1945.

2. Ambler, J. W.: Statistical Survey of Two Hundred Cases of Atypical Lichen Planus, in Report of the United States Army Medical Department, Dec. 16, 1944.

3. Bureau of Medicine and Surgery Letter, March 13, 1945 [confidential report].

was no evidence of lesions. Ten days later she noted a recurrence, for which she was given 20,000 units of penicillin intramuscularly every three hours for a total of 1,000,000 units, without benefit. She then returned to the use of the penicillin mouth wash with complete remission in four days. Since then she has had repeated relapses which have invariably responded within a few days to the use of the penicillin mouth wash.

CASE 2.—W. A. S., a 31 year old white housewife, complained of an eruption on the tongue of over fifteen years' duration. There were exacerbations and remissions, although a week seldom went by without the appearance of new lesions. She noticed some burning of the tongue when hot or highly seasoned foods were eaten. Diets, mouth washes and local applications had not been of value.

On the dorsum and sides of the tongue were several discrete and confluent round exfoliated patches, 1 cm. in diameter, with bright red centers and gray to pale yellow borders. Dental caries or signs of gingivitis were not present. Culture showed a mixed growth of *Micrococcus flavus* (one of the *Neisseria* group of organisms) and alpha prime hemolytic streptococci. Culture on Sabouraud's medium did not show growth.

She was given a solution containing 1,000 units of penicillin per cubic centimeter of isotonic solution of sodium chloride with instructions to use it as a mouth wash three to four times a day. Within twenty-four hours improvement was noted, and within four days her tongue was normal looking. Two weeks later she experienced a recurrence which again cleared with the penicillin mouth wash. Since then, from time to time, she has noticed new lesions which have always responded quickly to the use of the penicillin mouth wash.

The prompt response of these 2 patients to the local use of penicillin solution strongly suggests a bacterial causation. Streptococci were found in cultures from both tongues, although similar organisms are sometimes detected on routine mouth and throat cultures. It is also noteworthy that penicillin parenterally was ineffective in 1 patient, although it is possible that a larger total dose might have accomplished the same result as did the local use of the drug. Although penicillin mouth washes, as used in these 2 patients, seemed to correct the disorder only temporarily, it is such a comparatively easy, cheap and safe form of treatment for this otherwise recalcitrant disease, that its further trial is indicated.

#### SUMMARY

Two patients with transitory benign plaques of the tongue obtained prompt remission of their eruption with the use of a mouth wash containing 1,000 units of penicillin per cubic centimeter of isotonic solution of sodium chloride. Relief was temporary, but relapses promptly responded to repetition of the treatment. This observation suggests a bacterial causation for this disorder.

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#### TINEA CAPITIS

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Tinea capitis is prevalent in preadolescent youngsters throughout many sections of the country. Most of the infections in the locality of San Jose, Calif., are of the *Microsporum lanosum* variety and in general respond well to local therapy.

In addition to the various local applications I have been prescribing shampooing of the scalp at frequent intervals, making use of the sulfur foam cloths put out by the Wyeth Company. I prescribe one shampoo each day for the first

to the United States Navy, none of these reports appeared in print until after hostilities with Japan ceased.

Several significant articles have appeared since this time on this new clinical entity attributable to quinacrine hydrochloride.<sup>4</sup> Within these articles one can find a variety of clinical descriptions of this new disease, for the most part stressing its clinical similarity to lichen planus, its association with ingestion of quinacrine hydrochloride and its mixed occurrence with exfoliative dermatitis and eczematoid dermatitis. The original article of Schmitt<sup>1</sup> is exceptional.

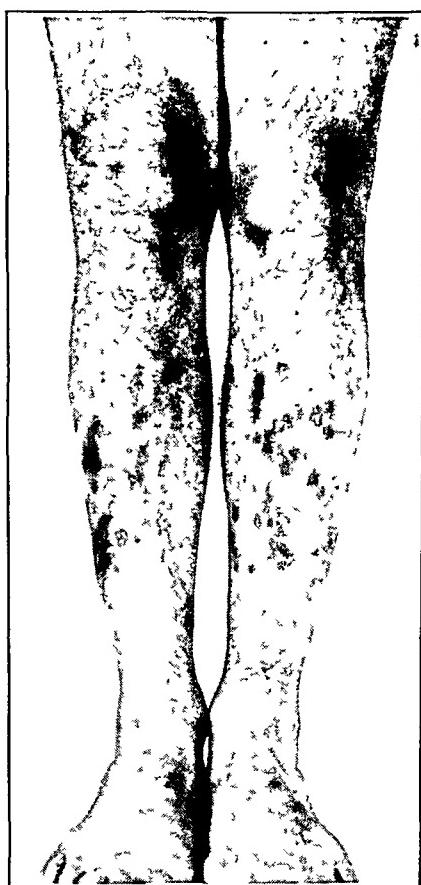


Fig. 1.—Atypical lichenoid dermatitis.

4. (a) Nisbet, T. W.: A New Cutaneous Syndrome Occurring in New Guinea and Adjacent Islands, *Arch. Dermat. & Syph.* **52**:221 (Oct.) 1945. (b) Bagby, J. W.: A Tropical Lichen Planus-Like Disease, *ibid.* **52**:1 (July) 1945. (c) Livingood, C. S., and Dieuaide, F. R.: Untoward Reactions Attributable to Atabrine, *Bull. U. S. Army M. Dept.* **4**:653 (Dec.) 1945; *J. A. M. A.* **129**:1091 (Dec. 15) 1945. (d) Epstein, E.: Lichen Planus-Eczematoid Dermatitis Complex of Southwest Pacific, *Bull. U. S. Army M. Dept.* **4**:687 (Dec.) 1945. (e) Goldberg, L. C.: Unusual Lichenoid Dermatoses, *J. A. M. A.* **130**:775 (March 23) 1946.

## Society Transactions

### LOS ANGELES DERMATOLOGICAL SOCIETY

Clement E. Counter, M.D., *Chairman*

Maximilian E. Obermayer, M.D., *Secretary*

Oct. 9, 1945

**Melanoma of the Nipple.** Presented for therapeutic suggestions by DR. A. K. JENSEN.

C. M. S., a white man aged 33, first became aware of a flat, smooth "mole" about 3 cm. below and 2 cm. medial to the left nipple. Because of progressive enlargement of the lesion he consulted a physician, who performed a biopsy. A histologic diagnosis of malignant melanoma grade II was made. He was first seen by the presenter at the dermatologic clinic of the White Memorial Hospital, on Sept. 13, 1945. At that time he presented an elevated, deep brown to black nodule about the size of a large pea. Part of the lesion showed scarring from previous removal of tissue for biopsy. There seemed to be some enlargement of the left axillary lymph nodes. Routine laboratory tests gave normal results.

The histologic section showed epithelial disintegration, with large masses of melanoblastic cells all through the dermis. A few nevus cells were present in the enlarged papillae.

**NOTE.**—A modified mastectomy was performed. Microscopic examination of the axillary lymph nodes showed only mild hyperplasia.

### DISCUSSION

DR. H. P. JACOBSON: The presenting clinical picture is that of a malignant melanoma. On examination of the axillas, I found that the left axillary space contained several fairly large, infiltrated nodes; in my opinion, the patient has a malignant melanoma with probable axillary metastasis. At the risk of meeting with criticism, I wish again to register my protest against performing biopsy on a melanotic lesion that suggests malignancy. I deem it bad practice, which now and then has tragic results. When a melanotic lesion has suspicious features justifying microscopic investigation, the only rational method of approach is complete, total and wide excision with cautery. Microscopic postexcisional evidence of malignancy calls for even more radical excision with cautery.

DR. H. C. L. LINDSAY, Pasadena, Calif.: Dr. Jacobson's statement that it is better to excise thoroughly a melanotic lesion by means of a cautery knife than to remove a small specimen for biopsy has been debated before. At several medical-surgical meetings his contention has been substantiated. Members of this society know well 2 cases in which subsequent surgical excision did not save the patient whose melanoma had been subjected to biopsy.

DR. A. K. JENSEN: From what Dr. Jacobson has said, it is well that I did not have a specimen taken for biopsy. I feel that it will make no difference now what kind of therapy is used, but I have presented the patient as a warning to myself and to others.

**Squamous Cell Epithelioma Developing in a Nevus.** Presented by DR. N. P. ANDERSON.

P. M., a white girl aged 8 years, had had a linear nevus on the left side of the nose along the inner canthus of the eye since birth. About two weeks before I first saw her a warty growth developed in the lowermost part of the nevus.

It appears from the cases reported in some of these articles, as well as the discussions and personal communications, that there exists much confusion as to just what are the clinical characteristics of atypical lichenoid dermatitis. It is the purpose of this communication to attempt a clear definition of this new disease, which appears to be a drug eruption as the result of prolonged ingestion of quinacrine hydrochloride, and to report a résumé of 60 cases which occurred among the personnel of the

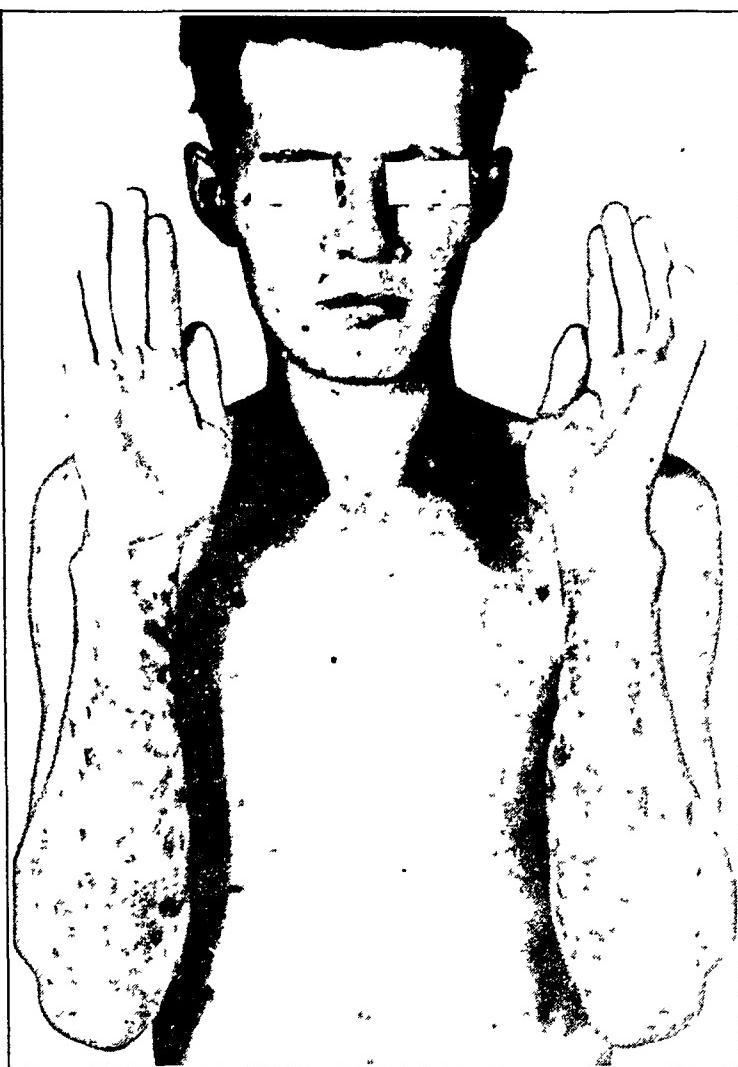


Fig. 2.—Distribution of the eruption.

Seventh Fleet, United States Navy, in 1944 and 1945. The variegated and polymorphic lesions clinically similar to exfoliative and eczematoid dermatitis will not be stressed, since, to us, it is not an integral part of the disease known as "atypical lichenoid dermatitis."

Atypical lichenoid dermatitis may be described as an essentially chronic progressive eruption, occurring oftenest in early middle age, due to the prolonged ingestion of quinacrine hydrochloride and precipitated by cutaneous irritation under conditions of unusual stress and strain.

DR. M. E. OBERMAYER: I lean toward the diagnosis of the deep granulomatous form of lupus erythematosus. The section showed follicular plugging, and the absence of plasma cells in the inflammatory infiltrate militates against the diagnosis of syphilitic granuloma.

DR. H. P. JACOBSON: I concur heartily with Dr. Goeckerman in his diagnosis. I think that this lesion is a nodular syphilid with a suggestive serpiginous outline. The dusky red color, too, is suggestive. The lesion, I believe, is neither lupus erythematosus nor granuloma annulare.

DR. H. H. WINER (by invitation): The microscopic section showed an area of lymphocytic infiltration surrounded by giant cells, which were numerous. This suggests to me a syphilitic process. The follicular plugging and epidermal atrophy, even though present, are due to pressure from the infiltration, which is more diffuse than is seen in lupus erythematosus. I did not note the intimal proliferation that I should like to see in a late secondary or a tertiary syphilitic lesion, into which type this lesion would fall. I suggest the diagnosis of a late syphilid, or possibly sarcoid.

DR. H. C. L. LINDSAY, Pasadena, Calif.: The induration of the lesion and the microscopic picture are suggestive of syphilis. The presence of giant cells in the specimen is not incompatible with such a diagnosis.

DR. MOLLEURUS COUPERUS: Clinically the lesion is nodular; it does not suggest lupus erythematosus strongly, nor to my mind does it look like granuloma annulare. It resembles more a syphilitic lesion. However, I must agree with Dr. Obermayer in the microscopic diagnosis and must confess that I did not see any giant cells. I feel that the microscopic picture is compatible with the diagnosis of lupus erythematosus.

DR. J. WALTER WILSON: I must admit that the microscopic picture is not that of a syphilitic lesion. I shall report the results of tests for syphilis.

NOTE: The Wassermann reaction was strongly positive, as were the Kahn, Kline and Eagle reactions. Antisyphilitic therapy resulted in prompt involution of the lesion.

#### Actinic Dermatitis Due to Roentgen Rays; Epithelioma? Presented by DR. JOHN D. ROGERS.

G. C., a white woman aged 41, has had an eruption on both hands at intervals for fourteen years and continuously for the past three or four years, during which time, the patient stated, she had had about forty treatments with roentgen rays.

The skin of the right hand is roughened and slightly erythematous, with a number of small verrucous lesions on the dorsum and a larger one on the fourth finger. The skin feels rigid, and there is limited movement of all fingers, especially the fourth. The palm and the dorsum of the left hand are involved to a less degree.

#### DISCUSSION

DR. WILLIAM MULVEHILL, Los Angeles: This case presented to me undoubted evidence of actinic dermatitis. There were atrophy and fixation of tissues and a history of receiving 2,500 r within approximately two years. I am inclined to think that the patient has an actinic epithelioma. She received fifteen exposures, of 165 r each, all but one within a period of two years; this was entirely too much. The total dose when 75 r is given at each exposure should not exceed 1,200 r, or 1,400 r at the very most. The only method of treatment is radical removal of the tumorous formation and observation, as other lesions are likely to develop.

DR. SAUL ROBINSON: I believe there are two enlarged lymph nodes in the axilla which should be removed and examined for possible metastasis. Several years ago I treated a patient with a squamous cell epithelioma on the forearm which metastasized to the axillary lymph nodes. The nodes were removed, and high voltage roentgen therapy was given later.

It usually begins with the appearance of one or more scaly pruritic areas, occurring most commonly on the feet, hands, groin or neck. These patches are composed of grouped lichen-planus-like papules, dusky red to purple, with a fine dry scale. Coalescence of these papules produces a flat lichenified plaque of a striking violaceous color (fig. 1). As these plaques enlarge, itching becomes a prominent symptom, and scratching, maceration from sweat and overtreatment often result in an exudative, weeping eruption. The distribution is oftener than not bilaterally sym-

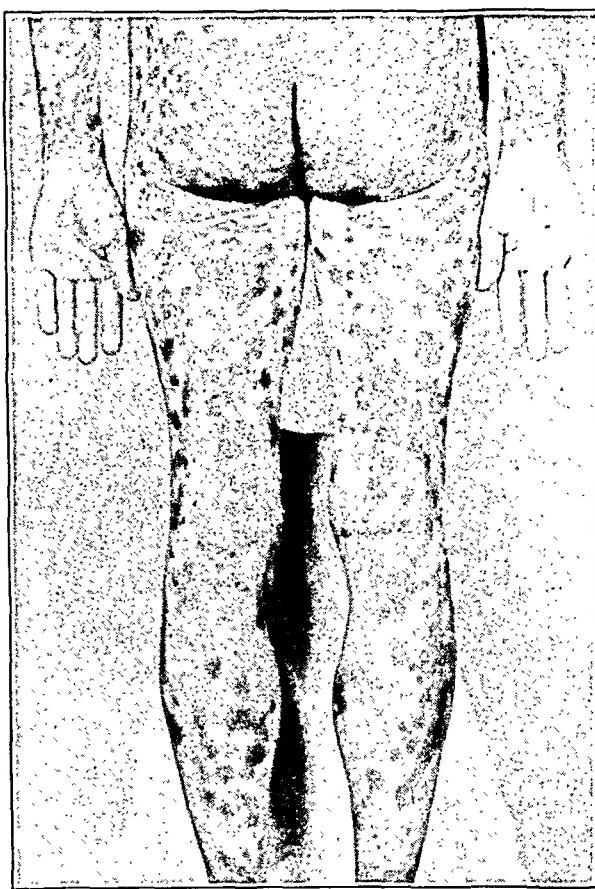


Fig. 3.—Distribution of the eruption.

metric; hence the term "symmetrical eczema" of Ambler.<sup>2</sup> The eruption may slowly regress and then reappear to progress into a dissemination to the legs, arms and body (figs. 2 and 3). The eruption notably occurs in such characteristic areas as the upper eyelids, tips of ears, scalp and lower lip (which is often blue) and the mucous membranes of the mouth (fig. 4).

In some patients the papules and plaques may become firm, hypertrophic nodules with a verrucous appearance, not clinically distinguishable from hypertrophic lichen planus. These nodules appear oftenest

in New York but claimed that no definite diagnosis was ever made. She had a series of roentgen ray treatments for "uterine fibroid" twenty-five years ago. Five years later a course of radium therapy was administered for the same condition. A cholecystectomy was performed in 1919. Her general health had been excellent until four years ago, at which time she began to have a series of digestive upsets. These have been fairly well controlled by a high intake of hydrochloric acid and bile salts.

Groups of vesicles on top of slightly raised erythematous papules are irregularly distributed over the knees and the dorsa of the feet.

The blood and the differential count were normal. Intradermal tests for hypersensitivity to foods gave negative reactions.

**Erythema Multiforme (Recurrent) with Herpes Simplex. Presented by DR. N. P. ANDERSON.**

H. B., a white woman of American stock aged 46, was first seen on Dec. 4, 1944. She had had a "cold sore" at the right commissure of the mouth for the preceding two weeks. One week after the herpes simplex first appeared there occurred a typical attack of erythema multiforme with lesions of herpes iris on both wrists and on the tongue.

She received three vaccinations for smallpox at intervals of two weeks.

The present attack began with herpes simplex on the left commissure of the mouth. Several days later the erythema multiforme appeared.

Erythematous lesions of the iris type are present on the dorsa of the hands and wrists, and a sharply circumscribed erosion, 2 cm. in diameter, covered with a fibrinous membrane is located on the undersurface of the tongue on the left side. Remnants of herpetic lesions are present on the oral mucosa near the left commissure.

**DISCUSSION ON PAPERS BY DRs. KETTENBACH AND ANDERSON**

**DR. SAUL ROBINSON:** I agree with the diagnoses in these cases. Within the last six months I have seen 6 or 8 patients with the association of herpes simplex and multiforme erythema, and I have noticed that repeated vaccinations for smallpox, as advocated by Dr. Anderson, constitute a satisfactory treatment.

**DR. SAMUEL AYRES JR.:** Since Dr. Anderson called attention to the association of herpes simplex and erythema multiforme (*Erythema Multiforme: Its Relationship to Herpes Simplex*, ARCH. DERMAT. & SYPH. 51:10 [Jan.] 1945), I have encountered several patients with that syndrome in the past year. Dr. Kettenbach's case is of a rather peculiar type which one encounters occasionally and which is hard to classify. The picture is not the ordinary one. It verges on that of dermatitis herpetiformis and also suggests erythema annulare centrifugum. It is probably closely related to erythema multiforme. I saw such a case about a year ago in which the erythema was much more extensive and occurred in a young man with ulcerative colitis. The cutaneous lesions flared up with exacerbations of his colitis.

**DR. JULIUS SCHOLTZ:** Most virus diseases are characterized by titratable antibodies in the blood. Sufficient cross reactions may occur so that a specific antigen is not necessary. I had read Dr. Anderson's article and wondered whether any studies in this direction had been done in his cases.

**DR. M. E. OBERMAYER:** I think that the lesions on the tongue in Dr. Anderson's case constituted aphthous stomatitis rather than herpes simplex.

**DR. FLORALOU KETTENBACH:** Needless to say, my patient presents a difficult therapeutic problem.

**DR. N. P. ANDERSON:** I saw my patient again this afternoon. It is obvious that the first therapeutic effort with vaccination for smallpox was not successful. I think that the herpes simplex in the outer corner of the mouth and the lesions on the tongue are all due to erythema multiforme. In my article, I was cautious not to ascribe a virus causation to erythema multiforme. I do not want any one

on the shins and the forearms. Regression of the eruption at this stage results in atrophy, scarring and surrounding dark brown pigmentation (fig. 5). Further progression of the disease results in the appearance of a grouped and disseminated follicular keratotic plugging, with production of follicular spines on the back, chest and posterior aspects of the arms, around the nasolabial folds and at the hair line of the scalp. In a few instances hard keratotic papules not unlike arsenical keratoses appear on the palms and soles (fig. 6). The eruption occurs on the

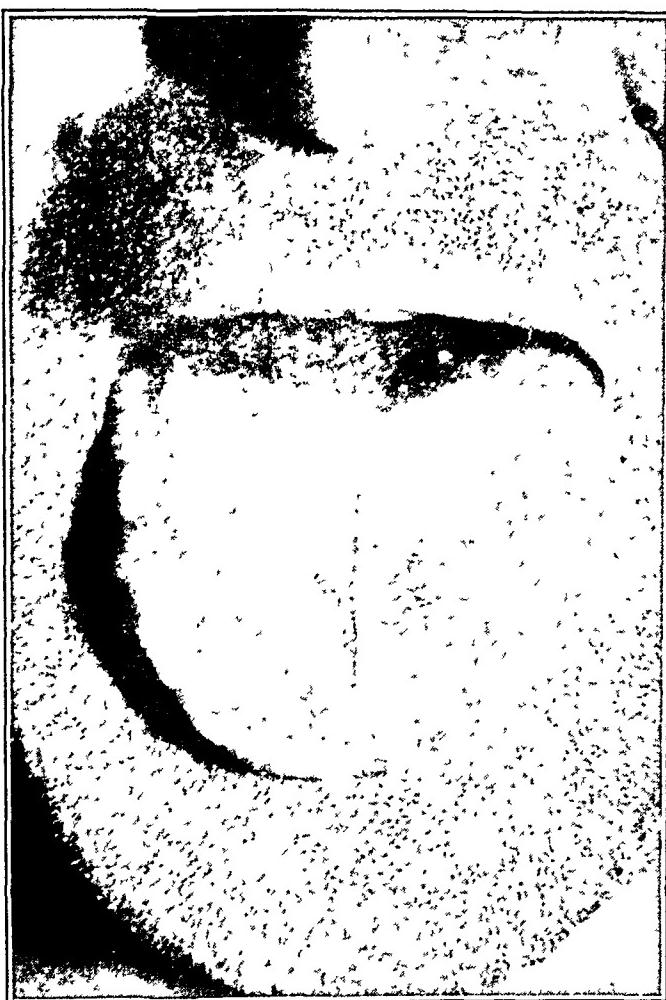


Fig. 4.—Leukoplakia of the tongue.

tongue and buccal mucosa as flat leukoplakic areas, and the lips, bluish (in striking contrast to the yellowish skin caused by quinacrine hydrochloride), are fissured and exudative. Often a moth-eaten alopecia results, and the nails become dry, brittle, thickened and fissured. The bluish, drop-shaped pigmentation of the nails often seen in users of quinacrine hydrochloride was seldom a component of the eruption.<sup>5</sup>

5. Lutterloh, C. H., and Shallenburger, P. L.: Unusual Pigmentation After Prolonged Suppressive Therapy with Quinacrine Hydrochloride, Arch. Dermat. & Syph. 53:349 (April) 1946.

The anterior two thirds of the glans penis is covered with a slightly elevated plaque, which is red and scaly with a denuded area of about 5 mm. There are no palpable inguinal lymph nodes. There is slight purulent moisture at the meatus.

Biopsy showed that, except for a small amount of round cell infiltration immediately below the epidermis and some capillary dilatation, the changes were entirely within the epidermis. There was much thickening of the rete pegs with virtual obliteration of the papillae. The epidermis showed polymorphism and polychromatism in its entire thickness and otherwise appeared to be malignant *in situ*. There were no typical Bowen or Paget cells.

#### DISCUSSION

DR. MILTON GOLDMAN, Van Nuys, Calif.: Microscopically I thought that this was an intraepidermal cancer. I was interested in the possibility of the lesion appearing in the site of a previous scar. Also, the patient had had a urethral discharge, which might be related to a malignant lesion of the urethra.

DR. L. H. WINER (by invitation): I agree with the diagnosis of epithelioma *in situ*, which is also known as Bowen's disease. It is characterized by nuclear clumping of the epidermal cells. The epidermis becomes acanthotic and thickened. In erythroplasia of Queyrat one sees oozing and weeping, which are not present in this case.

DR. M. E. OBERMAYER: I agree with the diagnosis of epithelioma *in situ* but object to the designation Bowen's disease, as the characteristic triad—individual cell keratinization, multinucleation and anaplasia—was not present in the section.

DR. H. P. JACOBSON: The presenting penile lesion is, of course, an intraepithelial cancer. Regardless of the label attached—Bowen's disease, Paget's disease or erythroplasia—the meaning is the same. It is a malignant neoplasm which is notoriously radioresistant. Eight or ten years ago, to the best of my recollection, an Englishman, Lewis, published an extensive article under the title "psoriasisiform epitheliomas," which covers this subject adequately. This label is especially applicable to the lesion in the present case, which strongly suggests a psoriasisiform plaque. The important desideratum as regards the patient is effective treatment, which, in my opinion, should consist of a radical operation. As I have already stated, these lesions are notoriously radioresistant. In view of the urethral discharge, urethroscopic studies should be undertaken before surgical intervention in order to determine the presence or absence of neoplastic involvement of the mucous membrane and to guide in the extent of the radical operation.

DR. J. WALTER WILSON: I have looked up the literature on erythroplasia of Queyrat and other intraepidermal malignant and premalignant lesions of the glans penis. I have not yet been able to obtain the original article by Fournier and Darier (*Bull. Soc. franç. de dermat. et syph.* 4:324, 1893) in 1893 or that by Queyrat (*Bull. Soc. franç. de dermat. et syph.* 22:378, 1911). The first report in this country was that of Sulzberger and Satenstein (*ARCH. DERMAT. & SYPH.* 28:798 [Dec.] 1933), and since that time several cases have been recorded. The histopathologic changes in these cases vary from acanthosis to frank intraepithelial carcinoma. In some cases the changes are typically those of Bowen's disease. The name "erythroplakia of Queyrat" seems to have arisen because of the histopathologic similarity to leukoplakia, but clinically the lesion is red instead of white. Later the term was changed to erythroplasia. The present case is without doubt one of intraepidermal carcinoma, or epithelioma *in situ*. Whether it can properly be called erythroplasia of Queyrat I cannot say as yet. The majority of the authors and commentators in the literature have expressed the opinion that the cells of this neoplasm are radioresistant. I believe that excision by cautery is the treatment of preference.

A Case for Diagnosis. Dermatitis Herpetiformis? Presented by MAJOR S. B. MAY, Medical Corps, Army of the United States (by invitation).

I. R. M., a white woman aged 27, of Polish-American stock, had had anemia at the ages of 5 and 11 years; splenectomy was performed at the age of 11. Since

The chronic lichenified plaques of the feet and hands are oftener than not preceded by or/and accompanied with a contact dermatitis or an eczematoid dermatitis.

There is no clearcut characteristic pathologic picture of atypical lichenoid dermatitis, but one can find in some portions of sections of



Fig. 5.—Atrophy, pigmentation and nail involvement.

the skin an inflammation not unlike that seen in lichen planus. The epidermis is acanthotic and the basal cell layer invaded and liquefied. There is often keratotic plugging at the sebaceous orifices. Vascularity is increased in the papillae, and a variety of cellular infiltrate is present, which extends into the reticular layers. Eosinophils are usually prominent, and there are usually many chromatophores laden with pigment.

**Leiomyoma Cutis.** Presented by DR. PAUL D. FOSTER.

J. R., a German aged 42, first noted the development of lesions over the epigastrium ten years ago; in the course of time more lesions developed, and during the past two or three years they have produced a mild, intermittent burning sensation.

Numerous bean-sized nodules are present over the epigastrium and extend onto the right flank. These are yellowish and firm and have a horizontal axis. They move freely with the skin. One lesion is of a dark erythematous color, and it is this nodule which currently causes a burning sensation.

Histologic examination disclosed smooth muscle extending in all directions, in many instances separated by islands of connective tissue. There was no indication, from the areas examined, of the origin of the smooth muscle.

**DISCUSSION**

DR. SAMUEL AYRES JR.: This is only the second case of its kind I have seen. The patient does not complain of tenderness, which is usually characteristic of this disease. The only other case I have seen was one originally reported by Dr. F. K. Frost. The lesions seem to be characteristic. In both cases they were located on the trunk, had a linear distribution and were brownish red.

DR. SAUL ROBINSON: About six years ago I treated a patient with leiomyoma cutis on the forearm. The lesion was destroyed locally by desiccation, with good results, and there was no recurrence.

DR. PAUL D. FOSTER: Microscopically the tumor is fairly typical of leiomyoma cutis.

**Superficial, Erythematous Basal Cell Epithelioma.** Presented by DR. IRVING BANCROFT.

A. W. S., a white man aged 69, has been in good health except for infection with syphilis twenty-five years ago, which was treated by means of mercurial ointment rubs and internal administration of potassium iodide. For the past twelve years he has had lesions on his back, which are said to have undergone little change. They are pruritic at times.

There are two lesions on the back. The lower, and more active, is oval, with a slightly erythematous and atrophic center and raised, erythematous borders. The upper lesion has the same appearance except that the erythema is less pronounced.

A serologic test of the blood gave a negative reaction for syphilis. Histologic examination showed a mass of "palisading" basal cells which extended deep into the dermis, where it was sharply demarcated and surrounded with mild lymphocytic infiltration.

**DISCUSSION**

DR. JOHN D. ROGERS: I agree with the diagnosis. The lesions resemble closely the type that is often associated with the previous use of arsenic. I do not know whether there is any history of exposure to arsenic in this case, but that is what the picture suggests to me. I think that irradiation, cautery or electrodesiccation would be effective.

DR. KENNETH STOUT: I have seen 3 similar cases of superficial epithelioma in the past several years, and in 1 case the lesion was of twenty years' duration and about 2 inches (5 cm.) in diameter. This lesion was given radiation for a total dose of 3,600 r about one and a half years ago, and it has remained healed to date.

DR. A. F. HALL JR., Santa Monica, Calif.: In my experience, the lesions which are often associated with the ingestion of arsenic are not radiosensitive to the degree that is expected in most basal cell epitheliomas. I have found them to be radioresistant and to need destructive measures.

DR. IRVING R. BANCROFT: I have advised the patient not to have anything done about this lesion, as it grows slowly. He is nearly 70 years old, and his circulatory system is inadequate. There is a possibility of arsenic having played an etiologic role, as he was a printer for many years.

There are usually some foreign body giant cells present. There are seldom the distinct islands of round cell infiltrate so characteristic of lichen planus (fig. 7).

An analysis of 60 cases as they appeared among the personnel of the Seventh Fleet will serve to illustrate the pertinent facts characteristic



Fig. 6.—Keratosis of the soles.

of this disease much more clearly than will the repetition of histories of cases already cited by others.<sup>6</sup>

Group examination of 47,990 men serving ashore and taking quinacrine hydrochloride routinely and of 3,000 men serving at sea and

6. Schmitt.<sup>1</sup> Footnote 4.

theliosis, Letterer-Siwe disease and Schüller-Christian disease are not different forms of the same malady. The essential feature of the disease is a granuloma-like proliferation of the cells of the reticuloendothelial system, which occurs for some unknown reason. If it occurs in infants and young children, the disease runs a rapid course of hemorrhagic diathesis and progressive anemia. There is proliferation of reticulum cells in the spleen, thymus, lymph nodes, liver and bone marrow, with hemorrhages and early death. In older persons the course is slower. Granulomas appear, and the symptoms depend on the localization of the proliferating cells. There is a tendency to involvement of the skull, mesencephalon, orbits, spleen and liver. Because of the long course of the disease the reticulum cells have time to ingest large amounts of cholesterol. Wallgren stated that attempts should be made to determine whether the diseases are not identical, for the symptoms regarded as characteristic of Letterer-Siwe disease are not foreign to atypical cases of Schüller-Christian disease and it is well known that there are many variants of the latter. Thus, the typical triad is that of diabetes insipidus, exophthalmos and xanthomatous lesions in bones. In some cases there is no diabetes insipidus; again, no exophthalmos; again, no osseous changes, and so forth. He thinks that if the patients with Letterer-Siwe disease lived long enough there might be lipidic changes too in the reticuloendothelial cells. The Cleveland Dermatological Society is greatly indebted to Prof. Charles McKhann, of the department of pediatrics, for presentation of the patient's history and for the opportunity to see the colored slides of the patient.

**Pemphigus Foliaceus.** Presented by DR. J. H. BARR JR. and DR. J. KAM for DR. H. N. COLE and DR. J. R. DRIVER.

A. A., a white woman aged 46, three years ago first noted a chronic erythematous squamous eruption, limited to the left temple. In spite of treatment with heavy metals, and symptomatic therapy, this gradually spread to involve the face and forehead. Three months before her admission there developed a bullous eruption, limited to the trunk, arms and thighs.

On admission, the eruption is symmetric and generalized. The face is involved in a crusted, seborrheic-like eruption, with a butterfly distribution over the nose and cheeks. The trunk, arms and thighs exhibit an eruption of mixed character. There are sparsely scattered seborrheic-like patches, flaccid bullae and impetiginous crusted lesions. On rupturing, the bullae are manifest by raw, denuded areas and lesions with an inflammatory base, covered with adherent crusts. There are no lesions of the mucous membranes and Nikolsky's sign is not present.

Complete urinalysis gave normal findings; the plasma proteins, the albumin-globulin ratio and the serum calcium and phosphorus were normal. A serologic test for syphilis gave a negative reaction. A hemogram revealed an erythrocyte count of 3,750,000, a hemoglobin concentration of 75 per cent and a normal leukocyte count, with 6 per cent eosinophils on differential count.

Histologic examination revealed acanthosis, erosion and vesicle formation in the epidermis. The superficial portion of the corium was edematous and stained intensely acidophilic. There was deep infiltration of the corium with mononuclear cells and an occasional polymorphonuclear leukocyte.

"Bismarsen," solution of potassium arsenite U. S. P. and sulfonamide compounds were administered, with no effect. The eruption became more extensive and changed in character from that of the pemphigus erythematosus (Senear-Usher syndrome) to that of pemphigus foliaceus. At present the plasma proteins, serum calcium and serum phosphorus are abnormally low. Nikolsky's sign is now present.

#### DISCUSSION

DR. J. H. BARR JR.: The chief thing of interest in this case is that when the patient came in the disease was typical pemphigus erythematosus and progressed to pemphigus foliaceus. At no time were there any lesions of the mouth.

not taking quinacrine hydrochloride revealed the following significant data:

1. The incidence of atypical lichenoid dermatitis among persons taking quinacrine hydrochloride was small—less than 0.6 cases per thousand men at a given time.
2. No cases were discovered among the men aboard ship not taking quinacrine hydrochloride.
3. The eruption occurred only in one instance among men who had been in the South Pacific and taking quinacrine hydrochloride for less than six months.



Fig. 7.—Photomicrograph of atypical lichenoid dermatitis. See description in the text.

4. The disease occurred in personnel outside the New Guinea-Solomon Islands areas (i. e., the Philippine Islands).
5. It was not associated with any evidence of food or vitamin deficiency.
6. It occurred most frequently among persons engaged in combat but did occur in men on duty far behind the combat zones.

Personal examination of some 600 native Melanesians in Middle Guinea and in the Biak (northwest New Guinea) areas and of native Filipinos did not reveal an eruption clinically comparable to atypical lichenoid dermatitis. A Filipino dermatologist (Dr. Guitierrez) recalled

staphylococci can be demonstrated. In this case there was a nearly normal epidermis with little vacuolation of cells near the stratum granulosum. There were a few small foci of lymphocytes around sweat glands. I could not see any evidence of nevoid changes or of infection.

DR. R. E. BARNEY: Clinically, the lesion seems to me to resemble a sarcoid. Unfortunately, trauma resulting from removal of the tissue for biopsy does not permit one to know what the lesion looked like before. I do not think one can make a definite diagnosis. There were not many changes. Some cells in the section—a particular group—suggested nevus cells, and there was a small amount of lymphocytic infiltration.

DR. H. N. COLE: I was certain it was not a granuloma pyogenicum, but I believe it belongs in the group of granulomas. I do not know the cause, but if the patient were mine I should treat the lesion with solid carbon dioxide.

**Nevus Pigmentosus et Pilosus.** Presented by DR. E. J. ARDAY.

P. C., a white boy aged 6 months, was born with a hairy nevus covering his entire back, from the nucha to the waist line, ending in a straight line at the level of the belt line and falling in a fairly straight line at both posterior axillary lines. This lesion was always covered with a fine furry growth of hair of dark brown color, giving the appearance of a fur vest.

About two months ago many macular, flat, light brown macules appeared on both extremities. Recently three faintly brown lesions have appeared on the face. In one of the newer lesions on the left ankle fine blond hairs have developed. Only the anterior aspect of the trunk is free.

**DISCUSSION**

DR. F. J. ARDAY: My purpose in having this patient come here was to get advice regarding treatment. Of course, the advice one could give the parents was far from satisfactory. The possibility of a malignant process developing later in life should be considered seriously. In an article by Traub and Keil (The "Common Mole," ARCH. DERMAT. & SYPH. 41:214 [Feb.] 1940) the location of nevi in relation to malignant growths is discussed. This patient shows some nevi which are not hairy and look more like freckles.

DR. E. W. NETHERTON: In patients with a nevus of this type lesions may in rare instances develop in the central nervous system and meninges and a melanocarcinoma may occur. Neurosurgeons are often interested in whether there is any connection.

**Atypical Lichen Planus (Dermatitis Medicamentosa Due to Quinacrine [Atabrine]).** Presented by DR. H. N. COLE and DR. J. R. DRIVER.

R. C. B., a white man aged 47, has never had any cutaneous trouble in the past and has been in good health. He has been in New Guinea for more than two years and took suppressive doses of quinacrine. Fifteen months ago an eruption appeared, accompanied with severe pruritus, loss of weight and attacks of fever. There was complete loss of all his hair. From time to time he has had multiple areas of infection, probably secondary to scratching.

There is a patchy type of alopecia, with keratotic lesions here and there in his scalp. The patient now has a certain amount of axillary hair, pubic hair and a little on other parts of the body. The hair of the head has a somewhat moth-eaten appearance, but it is now growing in. Spread over the body are superficial pigmented lesions with some areas suggesting slight atrophy of the skin. On the flexor aspects of the wrists and over the sternal area are violaceous, shiny papules, accompanied with a certain amount of desquamation. There are similar papules on the lower limbs. Scattered irregularly over the body are numerous verrucous nodularis.

## MINNESOTA DERMATOLOGICAL SOCIETY

S. E. Sweitzer, M.D., President

H. A. Cumming, M.D., Secretary

Nov. 16, 1945

Necrobiosis Lipoidica Diabeticorum. Presented by DR. FRANCIS W. LYNCH, St. Paul.

Mrs. A. G., aged 35, had noted an eruption on the left leg for four years, accompanied with swelling and periodic ulceration. The eruption was thought to have followed a bruise. The presence of diabetes had been recognized for fifteen years, and she took insulin regularly, though without adequate control by examinations of the urine.

On the anterior aspect of the left leg there is a firm, slightly inflamed, irregularly oval plaque, 3 by 6 inches (7.6 by 15 cm.), which is adherent to the underlying tissues. The surface is uneven, with a few crusted areas. Some portions of the eruption are red and others light yellow.

Necrobiosis Lipoidica Diabeticorum Without Diabetes. Presented by DR. JOHN F. MADDEN, St. Paul.

Mrs. A. L. L., aged 39, first noticed lesions appearing on the anterior surface of the middle third of the legs in 1942. Repeated urinalyses failed to reveal sugar. The fasting blood sugar was 92 mg. per hundred cubic centimeters.

She now has two olive-sized lesions on the right shin and three small, bean-sized lesions on the left shin. They are orange-yellow, slightly depressed, irregular, asymptomatic plaques.

Necrobiosis Lipoidica Diabeticorum. Presented by DR. JOHN F. MADDEN, St. Paul.

Mrs. J. R. L., aged 50, in the summer of 1940 noticed numerous bean-sized, flat plaques on her legs, which increased slightly in size. She had diabetes and took insulin. The urine showed 4.2 mg. of sugar per hundred cubic centimeters, and the fasting blood sugar was 219 mg. per hundred cubic centimeters.

Examination shows oval, flat plaques of orange hue on the legs.

## DISCUSSION ON CASES OF NECROBIOSIS LIPOIDICA DIABETICORUM

DR. HENRY E. MICHELSON, Minneapolis: Dermatologists often draw comparisons between the incidence of necrobiosis lipoidica diabetorum in preinsulin days and the present incidence. It is my feeling that insulin does not affect these lesions in any way, either in production or in cure. I saw a recent report of a lesion on the hand which assumed verrucous characteristics. I presume that eventually there will be a much better understanding of this disease.

DR. CARL W. LAYMON, Minneapolis: At various recent meetings there has been considerable discussion as to whether necrobiosis can occur in the nondiabetic patient. Most patients who have lesions clinically consistent with the diagnosis of necrobiosis lipoidica diabetorum and who do not have proved diabetes give a family history of that disease or have some abnormality in the dextrose tolerance curve. In Dr. Madden's case a dextrose tolerance test had not been made and might give interesting information.

DR. LOUIS A. BRUNSTING, Rochester, Minn.: I do not understand the relation of these lesions to therapy with insulin; it sometimes happens that the appearance of the lesions of the skin gives the first clue to underlying diabetes. It is my impression that when the diabetes is properly controlled there is recession of the cutaneous lesions.

definite worsening of the eruption followed its further ingestion. We observed no positive reactions to patch tests with quinacrine hydrochloride. Laboratory equipment was not available to determine plasma levels of quinacrine hydrochloride.

5. *Relation to Anemia.*—There was in no patient who was hospitalized any evidence of anemia or jaundice, and, as a whole, the men were remarkably hale and hearty. Most had lost some weight.

The distribution of the eruption and the appearance of the predominant lesions are in agreement with the findings of Ambler.<sup>2</sup> The main point of difference lies in the severity. In the cases occurring among the Army personnel the condition was, as a whole, much more severe and extensive than that occurring among the Navy men.

At one time it was thought that atypical lichenoid dermatitis was peculiar to the South Pacific areas, a few dermatologists considering that certain irritating flora in New Guinea (Australian gum tree) might be one of the precipitating factors. However, the disease has since been reported as occurring in the Indian and Mediterranean theaters.<sup>7</sup>

Evidence now appears to be overwhelming that the repeated ingestion of quinacrine hydrochloride in relatively large doses over long periods (approximately 1.0 Gm. a week for months) is a major factor in the production of atypical lichenoid dermatitis. However, there appears to be a "trigger mechanism" in the form of dermal injury, such as contact dermatitis, fungous infections, eczematoid dermatitis and emotional fatigue. The experimental work on men with quiescent eruptions of the disease done by Schmitt<sup>1</sup> and Harvey<sup>8</sup> in New Guinea, and by Bianco, Barksdale and Sulzberger,<sup>9</sup> in the United States, in reproducing the eruption after reingestion of quinacrine hydrochloride is significant in this regard. Apparently the quantity of quinacrine hydrochloride in the plasma had little to do with the severity or extent of the eruption,<sup>8</sup> but there was obvious improvement of the patient as the plasma level of quinacrine hydrochloride diminished.

It is obvious from reports published previous to wartime experiences by Nayudu, Storey, Noojin and Callaway<sup>10</sup> that quinacrine hydrochloride will produce a generalized erythematous eruption and even

7. Whitehill, R.: Skin Sensitivity Due to Atabrine, Bull. U. S. Army M. Dept. 4:724 (Dec.) 1945. Nelson, L. M.: Dermatitis from Atabrine, ibid. 4:725 (Dec.) 1945.

8. Clinical and Laboratory Studies of Atypical Lichen Planus with Particular Reference to the Role of Atabrine, Report no. 13, Malaria Research Unit.

9. Bianco, A. A., and others: Tropical Dermatitis: Preliminary Report of Observation on Twelve Cases, Appendix 1, in Bureau of Medicine and Surgery Letter, March 13, 1945 [confidential report].

10. Nayudu, R. V. M.: Malaria and Its Treatment with Atabrine and Plasmochin, Indian M. Gaz. 72:531 (Sept.) 1937. Storey, W. E.: Toxic Exanthem

## DISCUSSION

DR. HENRY E. MICHELSON, Minneapolis: I think more histologic studies should be made. As I recall it, in alopecia areata the hair follicle is present but the hair is not, but I have not made any biopsies in a long time.

DR. CARL W. LAYMON, Minneapolis: I agree with the diagnosis. In textbooks it is noted that folliculitis can be seen early in the course of pseudopelade. Most patients, however, do not consult a physician at the beginning of the disease; so at the time of examination all one finds is loss of hair and scarring.

**Nevus Unius Lateris.** Presented by DR. JOHN F. MADDEN, St. Paul.

P. K., a girl aged 16, has a verrucous linear nevus extending from the middle portion of the posterior surface of the upper third of the left thigh down the leg to the heel.

## DISCUSSION

DR. CARL W. LAYMON, Minneapolis: In my opinion this is not a verrucous nevus. The diagnostic possibilities are linear psoriasis, lichen planus and lichen striatus. I favor the last diagnosis and believe that the prognosis is good.

DR. LOUIS A. BRUNSTING, Rochester, Minn.: In addition to the diagnoses Dr. Laymon has mentioned, I believe that ichthyosis hystrix should be considered. I could not identify nevus cells in the microscopic section. The disease is of such short duration and so mild that I cannot understand why it upsets the patient so.

DR. CARL W. LAYMON, Minneapolis: Senear and Carroll, in their study of lichen striatus, considered the several theories concerning linear localizations of the various diseases. They stated the belief that the most likely explanation of such lesions is the existence of certain zones of cutaneous fragility, perhaps on a hereditary basis. Lichen striatus occurs predominantly in children, but occasionally in adults.

DR. JOHN F. MADDEN, St. Paul: The patient has used many local applications, and the inflammation may have been caused by the drugs.

**Basal Cell Epithelioma, Morphea Type.** Presented by DR. JOHN F. MADDEN, St. Paul.

Mr. E. A. G., aged 23, noticed the appearance of a pinhead-sized papule on the right side of his chin about twelve years ago. The lesion has grown slowly since then.

The lesion is an asymptomatic, shiny, depressed, white plaque, about 3 cm. in diameter.

## DISCUSSION

DR. HENRY E. MICHELSON, Minneapolis: Clinically this did not appear to be an epithelioma, but microscopically there were little strands of cells that looked like basal cells. However, it may be found that these strands are not of basal cells at all; they may be remnants of hair follicles. I recall a report on a study representing many sections of a series of epitheliomas of this type; in these sections there was a good deal of epithelium with no downgrowth from the epithelium proper. If one were to study all the cases in which the lesion was reported as the morphea type of epithelioma, one might be surprised at the results. I think that many conditions are erroneously reported under that heading. My conception of the lesion is a superficial, peripherally extending and centrally healing epithelioma in which white scar is formed, with some activity always present within the scar. The microscopic diagnosis is usually basal cell epithelioma.

DR. CARL W. LAYMON, Minneapolis: This patient's lesion began at the age of 10 years and is progressing extremely slowly. In a case clinically similar to this which I recently observed, the growth proved to be a nevus of the hair follicle.

Nodular formation is more common in morphea than in generalized scleroderma. I did not think the third case (Mrs. C. P. W.) could be regarded as an instance of generalized scleroderma but was unable to make a definite diagnosis. Stains for mucin might give additional information, and a diagnosis of scleroderma adulorum should at least be considered.

DR. LOUIS A. BRUNSTING, Rochester, Minn.: In the first case (Mr. C. O. J.) the skin of the face, especially above the mouth, shows a peculiar wrinkling and waxy discoloration, like changes seen in senile elastosis, or even lipid proteinosis.

DR. RUBEN NOMLAND, Iowa City: I did not think the appearance was that of senile elastosis, but I have no diagnosis to offer.

DR. STEPHAN EPSTEIN, Marshfield, Wis.: There seems to be a somewhat fatalistic attitude in regard to the treatment of generalized scleroderma. I realize that it is difficult to draw definite conclusions because the number of cases one sees is rather small and spontaneous remissions occur. Nevertheless, I am under the impression that proper treatment has helped considerably in some of my cases. Regular, vigorous massage of the affected limbs, either by the patient or by some member of his family, and regular exercise in a warm bath seem of definite benefit. An ointment, 2 per cent ichthammol and 20 per cent cod liver oil in wool fat and petrolatum base, was used to massage the affected skin twice a day. Ointments emitting alpha rays appeared beneficial in a number of cases both of the localized and of the generalized type (*Arch. f. Dermat. u. Syph.* 167:533-542, 1933). These methods should be combined with roentgen treatment of the spine and the general supportive measures indicated in the particular case. Such a regimen may produce gratifying improvement in the function of the affected limbs. It is obvious that such management has a definite psychologic factor, but I do not believe that the results are all due to psychotherapy.

DR. CARL W. LAYMON, Minneapolis: Several years ago Gougerot and his associates reported cases of extreme dysphagia due to fibrosis of the esophagus in diffuse scleroderma. Cardiac and pulmonary fibrosis were also observed in these cases, and gastric lesions were demonstrated by means of gastroscopy.

DR. FRANCIS W. LYNCH, St. Paul: Some internists regard the internal changes as highly characteristic of the disease; the cardiac changes are thought to be diagnostic. When examined with Wood's (nickel oxide) light, patients with scleroderma present unusual changes, as described by Gougerot several years ago. It is possible to recognize lesions which are not visible in daylight; this observation will permit biopsy at an earlier stage of the disease, perhaps increasing understanding of the disorder.

#### Kraurosis Vulvae. Presented by DR. JOHN F. MADDEN, St. Paul.

Mrs. H. S., a housewife aged 53, stated that she had had itching of the vulva for the past ten years. She was seen at the Ancker Hospital in the fall of 1940, at which time the external genitals were atrophic and excoriated. She was given superficial roentgen therapy and antipruritic applications. This produced little change, and a vulvectomy was performed in May 1941. Improvement did not follow the vulvectomy, and the pruritus became increasingly severe. Recently the patient experienced relief from the use of a preparation the active analgesic of which is ethyl aminobenzoate.

The eruption involves the vaginal orifice, perineum and anal region, showing excoriated and atrophic white plaques.

#### DISCUSSION

DR. CARL W. LAYMON, Minneapolis: In my opinion, this is a case of lichen sclerosus et atrophicus rather than of kraurosis vulvae. There was a patch of lichen sclerosus et atrophicus over the left clavicle.

DR. LOUIS A. BRUNSTING, Rochester, Minn.: I agree with Dr. Laymon; there was characteristic distribution of the lesions in a zone around the vulva and anus.

for this reason that the features of what seemed to be permanent atrophy, hyperpigmentation, reticulated depigmentation and telangiectasis appeared to be more prominent in our cases than in his.

Physicians or other persons unacquainted with the facts and vagaries of drug eruptions naturally found it difficult to accept the causal role of quinacrine hydrochloride in these eruptions. The arguments which the skeptics first presented were arguments which one might have used against the drug causation of almost every proved form of drug eruption. Thus, for example, some observers caviled over the fact that so few of the many persons who ingested the drug got the eruption; yet it is known that this is true of most other drug eruptions as well, as, for example, the classical arsenical, salicylate or phenolphthalein eruptions. Others marveled that the disease took so long to disappear after the last exhibition of the drug; yet it is known that this is true of many other drug eruptions, such as those due to arsenic, iodides and bromides. And, again, like practically all other forms of drug eruptions, the reactions to quinacrine hydrochloride have once more demonstrated that there must be not only the exposure to the potentially more harmful drug but also the additional predisposing and contributory unknown factors operating at the time of exposure. And beyond the vague concepts of individual predisposition and contributory environments and local factors, the factors in eruptions from quinacrine hydrochloride are unknown.

In my efforts to formulate my thoughts on some possible unknown factors in the eruptions from quinacrine hydrochloride, I came to the conclusion that the important factors which all these patients had in common were the prolonged exposure to quinacrine hydrochloride plus prolonged activities in a tropical climate. Whether the cases occurred aboard ship or ashore, on good diets or bad, the men were all taking suppressive or therapeutic quinacrine hydrochloride while in the tropics and they all had in common the two great influences of long-lasting exposure to heat and to quinacrine hydrochloride. That brings up one point which I think Major Harvey Blank was the first to call to my attention and to the attention of the medical profession in general; and that is that a large number of these patients, perhaps well over half of them, show a generalized anhidrosis, a generalized lack of sweating, and that this anhidrosis persists for many months even after their last exposure to the drug.

I am sure that you are all acquainted with the tropical anhidrosis which was described in this country first by Wolkin, Goodman and Kelley (*J. A. M. A.* **124**:478 [Feb. 19] 1944) and in Australia by Allen and O'Brien (*M. J. Australia* **2**:335 [Sept. 23] 1944). Dr. Zimmerman, Dr. Emerson and I, working in Commodore Thomas Rivers' Naval Medical Research Unit no. 2 on Guam, were able to show that this form of tropical anhidrosis is not attributable to an exhaustion of the sweat-secreting apparatus, to a nervous mechanism or to any deep underlying, obscure cause but was directly and essentially connected with a horny plugging of the orifices of the sweat glands (*J. Invest. Dermat.* **7**:153 [Aug.] 1946). Moreover, Zimmerman and I had been able to show that this same plugging which is seen in tropical anhidrosis in a generalized form occurs in patches as an essential lesion of ordinary prickly heat (*J. Invest. Dermat.* **7**:61 [Feb.] 1946).

Thus, when the lesions of prickly heat become generalized, in some persons the whole body surface except the face and neck becomes incapable of pouring out sweat, and they suffer from tropical anhidrotic asthenia. Except on the face and neck, every one of the sweat glands is plugged, and it is this plugging which prevents the escape and evaporation of the cooling fluid. The patients are like a car with an empty radiator or broken fan belt.

A histologic section from an early lesion showed slight dyskeratotic change and the characteristic vesicular tendency in the epidermis.

## DISCUSSION

DR. RUBEN NOMLAND, Iowa City: Why is the name pemphigus used?

DR. FRANCIS W. LYNCH, St. Paul: I continue to use the term pemphigus because of the Haileys' early paper, rather than because of any strong belief that the eruption is closely related to pemphigus vulgaris. It has some resemblance to pemphigus erythematosus, described by Senechal and Usher.

**A Case for Diagnosis (Granuloma Annulare?).** Presented by DR. JOHN F. MADDEN, St. Paul.

R. B., a boy aged 5 years, had the appearance of annular, slightly pruritic lesions in September 1945. There was no evidence of tuberculosis in the patient or in his family.

Examination shows numerous annular lesions, 2 to 3 cm., on the ankles, thighs, buttocks, back and right ear. The borders are elevated and appear to be made up of individual papules. The centers of all lesions are depressed and in some instances covered with a fine scale.

## DISCUSSION

DR. RUBEN NOMLAND, Iowa City: I think that lesions of granuloma annulare if stained for fat would reveal a microscopic picture similar to that of necrobiosis lipoidica diabetorum. I have studied 2 cases of typical granuloma annulare in which there was a fatty infiltration similar to that of necrobiosis lipoidica diabetorum. I have also seen a case of indefinite papulonodular lesions on the ear sections of which showed a microscopic picture essentially the same as that of necrobiosis lipoidica diabetorum. It is my belief that the necrobiotic reaction is not limited to necrobiosis lipoidica diabetorum but is a nonspecific response to necrobiosis of the connective tissue.

I have seen necrobiotic changes associated with granuloma annulare and with one other disease. I believe the younger the lesion the more likely is fat to be present in the section. The old lesions that have gone on to epithelioid changes are not likely to show it.

**Lichen Planus.** Presented (by invitation) by DR. RODNEY F. KENDALL, St. Paul.

Mr. H. A. D., aged 26, first noted lesions on the penis and wrist in May 1945; they became generalized about July 20, 1945 and increased in number and extent until the first part of September.

Examination shows violaceous, angular papules with light scale over the entire body except for the palms, soles and face. On the scapular area and over the abdomen are areas of melasma where involution of the lesions took place. There are scaly, hypertrophic plaques on the legs. On the mucous membranes of the cheek is a lacy white network.

Treatment has consisted of oral administration of yellow mercurous iodide and fractional doses of low voltage roentgen therapy.

## DISCUSSION

DR. HENRY E. MICHELSON, Minneapolis: I was struck by the extent of the eruption in this case, and I think it looks like a dermatitis medicamentosa in cases I have seen. This patient told me that he took quinacrine, but was not in a malarial zone during the war and stopped taking the drug six months before the onset of symptoms.

**Junction Nevus.** Presented by DR. JOHN F. MADDEN, St. Paul.

Mrs. L. E. D., a housewife aged 66, stated that she had had a pigmented lesion on the left side of the face for the past ten years. It had gradually increased to the size of a silver dollar over this period.

I should now like to ask the following questions: Is it possible that such plugging of the pores may occur in the anhidrosis associated with atypical lichenoid dermatitis due to quinacrine hydrochloride? And, if so, is it conceivable that this plugging may have occurred first, i. e., before the eruption from quinacrine hydrochloride, as the result of long exposure to tropical heat and prickly heat? And is it possible that this plugging in turn predisposes to quinacrine hydrochloride dermatitis in some of these persons by preventing the normal excretion of quinacrine hydrochloride through the sweat? Is it possible, on the other hand, that the cutaneous reaction to quinacrine hydrochloride is in itself the cause and not the result of the anhidrosis, either through producing an irritation and plugging of the sweat pores or via other mechanisms?

These questions indicate the direction of studies which may be of help in ascertaining the nature of some of the unknown factors contributing to the pathogenesis of the eruptions due to quinacrine hydrochloride.

DR. ARTHUR R. WOODBURN, Denver: I should like to take just a few minutes to give a little of the other side of this story. I have had a large army service in dermatology in this country, and I have talked to a good many of the other men who have had such a service. I am basing these few observations on about 400 cases of this condition which my colleagues and I saw at Fitzsimons General Hospital during the war, mainly during the last eighteen months or two years.

We believe that quinacrine hydrochloride definitely produces the pigmentary changes. It produces the general yellowing of the skin, the transverse band across the nails, the transverse band across the sclera and conjunctiva, the pigmentation of the gingiva and a peculiar oval bandlike pigmentation of the hard palate. It also produces dermatitis venenata, and our experience leads us to believe that this was produced in this way: that men sweat, and as they sweat they excrete quinacrine hydrochloride in the sweat, which sensitizes the epidermal cells; this probably is the basis for the general exfoliated dermatitis which develops. An anemia develops which is a peculiar anemia, usually relieved by blood transfusions but often stubborn.

As to the cause of this lichenoid dermatitis, it is my opinion that quinacrine hydrochloride, while it may have some bearing, is not the most important point. I think that the point which Dr. Sulzberger was working on, the obstruction of the sweat apparatus and similar factors, is much more important. We felt that the mechanism was largely that of hyperhidrosis, dyshidrosis, anhidrosis, secondary infection and then general eczematoid reaction to infection. We felt this for these reasons: that among these many patients all of them improved on the way back on the boat, in spite of the fact that they all took quinacrine hydrochloride until they got to California. That is, they were on the boat for a month, six weeks or two months, during which their eruptions improved or in many cases completely disappeared, despite the fact that the men continued to take quinacrine hydrochloride.

In many of these men while on our service during the course of the treatment of this disease malaria developed, for which they were treated with quinacrine hydrochloride, and in only rare instances did we see any flare-up in the eruption.

About eighteen months ago the Army directed that all patients with malaria should take quinacrine hydrochloride prophylaxis for ninety days thereafter; this was instituted in all these cases, without notable flare-up.

In going through the literature we found a report from Malaya, a survey of dermatoses in Malaya, in which a similar eruption was reported in persons not taking quinacrine hydrochloride.

Those are our four reasons for feeling that probably ingestion of quinacrine hydrochloride is not the most important point but that sensitization to superficial infection is.

## Book Reviews

**An Atlas of the Commoner Skin Diseases.** By Henry C. G. Semon, D.M., with photography under the direction of Arnold Moritz, B.A., B.C. Third edition. Price, \$12. Pp. 339, with 139 plates. Baltimore: Williams & Wilkins Company, 1946.

This atlas is arranged so that all plates occupy entire right hand pages, while brief descriptions of the disease, differential diagnosis and treatment are on the left hand pages. The pages,  $9\frac{3}{4}$  inches by 7 inches (24.8 by 17.8 cm.), are large enough to include plates of sufficient size to present properly each disease. The diseases are arranged in alphabetical order, except that some of the less common ones have been placed at the end.

All plates are in natural color and for the most part they are excellent. The arrangement of the subjects, the exclusion of distracting nonessential material from the background and the lighting are, almost without exception, well done. As one might expect, there are a few plates, such as the plate illustrating tinea circinata, that are definitely inferior to the others in the atlas.

The author emphasizes that this is an atlas and that the description of the disease, the differential diagnosis and the treatment accompanying each plate is necessarily brief. It cannot take the place of the standard textbook. While the treatment recommended for the various diseases is conservative, it is felt by the reviewer that by the time the book went to press certainly such outstanding drugs as BAL (2,3-dimercaptopropanol), for the treatment of eruptions due to heavy metal, and calciferol (vitamin D<sub>2</sub>), for lupus vulgaris, had sufficiently demonstrated their usefulness to be included. It is noted that bromides are recommended as proper sedatives for use in the treatment of rosacea. Almost certainly the daily dosage of 10,000 units of vitamin A which is recommended for the treatment of keratosis follicularis is a typographic error. In this book eruptions due to the application of drugs, such as mercury or iodine, are called dermatitis medicamentosa, whereas American dermatologists use this term only for eruptions due to the ingestion, injection or absorption of a medicinal agent.

Many dermatologists will disagree with some of the treatments recommended or feel that some treatments have been omitted that have proved to be of definite benefit. Some dermatologists will disagree with some of the statements made elsewhere in the atlas. In spite of this, it is felt that the atlas will be of benefit to students, general practitioners or specialists in dermatology.

**The Control of Venereal Diseases.** By R. A. Vonderlehr, M.D., and J. R. Heller Jr., M.D. Fabricoid. Price, \$2.75. Pp. 246, with no illustrations. New York: Reynal & Hitchcock, Inc., 1946.

This book is a frank survey of the problem of controlling venereal disease. It is a logical successor to two previous works dealing with venereal disease: first, the heroic "Shadow on the Land," written in 1937 by Thomas Parran, M.D., and then, four years later, "Plain Words About Venereal Disease," by Parran and Vonderlehr.

This volume contains fifteen chapters on the progress made in bringing the subject of venereal disease to public attention, a brief sketch of the nature and treatment of gonorrhea and syphilis, the important problem of case finding and, finally, the task of prevention. The authors properly point out the emergency measures that were necessary during the war to control venereal disease. Admittedly, these were adopted for a short range program, with special emphasis placed on chemical prophylaxis and little effort made toward moral training. There is a comprehensive account of venereal disease control as exercised during the war years, and, as is pointed out in the foreword by Thomas Parran, "Its major contribution is the projection of wartime effort into a peacetime program."

DR. RICHARD L. SUTTON JR., Kansas City, Mo.: I had the view of this disease that the medical officer in a general hospital of the Zone of the Interior had. What must be believed of the varying descriptions are the observations, but the interpretations are what give a right to doubt.

I can confirm what Dr. Woodburne has just said regarding the failure of many patients to have flare-ups, even though they kept on taking quinacrine hydrochloride. During the time that the army directives insisted that quinacrine hydrochloride be given to all men back from malarial districts, the patients got well. When the physicians were ordered not to give quinacrine hydrochloride to these patients, they went on getting well in the same proportion, not a notably different rate. I never saw a flare-up when the drug was given to a patient with this disease, although other persons have seen it, undoubtedly.

When the exacerbation has occurred, it has not been the sudden sort of exacerbation that a dose of phenolphthalein will provoke in a patient who has a fixed eruption from phenolphthalein. Such a patient has a flare-up within a matter of hours, conspicuously.

I must take issue with the generality that there was no evidence of dietary deficiency, for in all the patients that I saw who were soldiers from the Southwest Pacific the story was classically that after six months or so on C rations, after they had lost 30 pounds (13.6 Kg.) (as they all did), their disease came on. The hospital dietitian, reading the list of nutrients available in C rations, insisted that the patients had not a vitamin deficiency, but the soldiers themselves got exceedingly fed up on "dog biscuits" and limited their diets to coffee and bread if they were available, for they could stomach them and not the other; I felt that they did have dietary deficiencies of some sort or other.

In a number of patients my colleagues and I found a low total protein content, of 5.5 Gm. per hundred cubic centimeters, or even as low as 5 Gm., and in some, but by no means all of these—and it was open to question as to whether the finding was laboratory error, but nobody else in the hospital complained of laboratory error—we had an increase of the albumin-globulin ratio, a ratio of 4.0, of 3.5 or a figure similar to that, indicating that the globulin level was down and the albumin content up. That is such an unusual finding that one has a right to doubt the laboratory.

I felt confident that heat, sweating and anxiety must be concerned, although quinacrine hydrochloride certainly played some sort of significant part. The ordinary evidence of intolerance of quinacrine hydrochloride is diarrhea. It is conceivable that quinacrine hydrochloride interferes with the absorption of nutrient (not necessarily vitamins) from the gastrointestinal tract. I know positively of patients in the China-Burma-India Theater who returned to the coast and, while waiting to be picked up and returned to the Zone of the Interior, discontinued taking quinacrine hydrochloride but continued having lichen planus or whatever this disease will be called, and shortly after the patients got on shipboard the eruption cleared promptly; so that cessation of use of quinacrine hydrochloride and continuance of unsatisfactory diet resulted in continuation of the disease, and adequacy of diet was followed by disappearance of the disease.

I saw at least 1 clearcut case from Italy. Consultants from the Surgeon General's Office were dubious of it, but I myself was satisfied that it was a case.

Quinacrine hydrochloride dermatitis was often complicated by infectious eczematoid dermatitis. I would get patients in by litter, by air; from New Guinea, oozing from head to foot. When streptococcal and staphylococcal infections were dealt with, the patient would then manifest straightforward quinacrine hydrochloride disease. In every case in which I saw alopecia, whether it was complicated by

# Directory of Dermatologic Societies \*

## INTERNATIONAL

### TENTH INTERNATIONAL CONGRESS OF DERMATOLOGY AND SYPHILOLOGY

Oliver S. Ormsby, President, 25 E. Washington St., Chicago.  
Paul A. O'Leary, Secretary-General, 102-2d Ave. S.W., Rochester, Minn.  
Place: New York. Time: Postponed indefinitely.

### PAN AMERICAN MEDICAL ASSOCIATION, SECTION OF DERMATOLOGY AND SYPHILOLOGY

J. J. Eller, President, 745-5th Ave., New York.  
Austin W. Cheever, Secretary, 464 Beacon St., Boston.

## FOREIGN

### CANADIAN DERMATOLOGICAL ASSOCIATION

Andrew M. Davidson, President, 6 Medical Arts Bldg., Winnipeg, Manitoba.  
W. George Brock, Secretary-Treasurer, 413 Medical Arts Bldg., Winnipeg,  
Manitoba.

### NORTH BRITISH DERMATOLOGICAL SOCIETY

President: Senior dermatologist in whichever city a meeting is convened.  
G. A. Grant Peterkin, Secretary, 4 Walker St., Edinburgh 3, Scotland.

### ROYAL SOCIETY OF MEDICINE, SECTION OF DERMATOLOGY

M. Sydney Thomson, President, 106 Harley St., London W. 1, England.  
F. R. Bettley, Secretary, 21 Harley St., London W. 1, England.

### SOCIEDAD MEXICANA DE DERMATOLOGÍA

Mario Salazar Mallén, President, Ignacio Ramírez 11, México, D. F., Mexico.  
Fernando Latapí, Permanent Secretary, Zacatecas 220-6, México, D. F., Mexico.

## NATIONAL

### AMERICAN MEDICAL ASSOCIATION, SCIENTIFIC ASSEMBLY, SECTION ON DERMATOLOGY AND SYPHILOLOGY

Henry E. Michelson, Chairman, 825 Nicollet Ave., Minneapolis, Minn.  
Clinton W. Lane, Secretary, 508 N. Grand Blvd., St. Louis 3.

### AMERICAN ACADEMY OF DERMATOLOGY AND SYPHILOLOGY

George M. MacKee, President, 999-5th Ave., New York.  
Earl D. Osborne, Secretary, 471 Delaware Ave., Buffalo 2, N. Y.  
Place: Hotel Statler, Cleveland. Time: Dec. 8-12, 1946.

### AMERICAN BOARD OF DERMATOLOGY AND SYPHILOLOGY

C. Guy Lane, President, 416 Marlborough St., Boston.  
George M. Lewis, Secretary-Treasurer, 66 E. 66th St., New York.

### AMERICAN DERMATOLOGICAL ASSOCIATION

Fred D. Weidman, President, Medical Laboratories, University of Pennsylvania,  
Philadelphia.  
Harry R. Foerster, Secretary, 208 E. Wisconsin Ave., Milwaukee.

### SOCIETY FOR INVESTIGATIVE DERMATOLOGY

Henry E. Michelson, President, 715 Medical Arts Bldg., Minneapolis.  
S. William Becker, Secretary, 55 E. Washington St., Chicago 2.

\* Secretaries of dermatologic societies are requested to furnish the information necessary for the editor to make this list complete and to keep it up to date.

infectious dermatitis or not, there eventuated regrowth of the hair, and, while scarring occurred in some areas of skin in these patients, the scarring was of a quality not incompatible with regrowth of follicles. Histologically, I saw that the inflammation seemed remarkably superficial. Even in ulcerative lesions where palpation suggested that the lesion would be thick histologically, inflammation was limited to the upper half of the dermis, and the inflammation apparently was so intense as to lift off the epithelium at that place; otherwise these lesions did not differ importantly from ordinary lichen planus.

Bismuth salicylate, given to the patients on the surmise that it sometimes helps lichen planus, did not help them, but thio-bismol did. I was interested in the study of the sulphydryl group, but my investigation was interrupted.

Louis Schwartz has identified cases of this dermatosis in workers in the manufacture of quinacrine hydrochloride who took in a great amount of the chemical apparently by inhalation. Some French reports, dated around 1935 or so, read exactly like those of these cases, and I feel sure that they saw cases such as we saw that did not have any connection with quinacrine hydrochloride. The blue pigmentation that is often associated here might have some relationship to the chemical similarity between methylene blue and quinacrine hydrochloride.

DR. HAMILTON MONTGOMERY, Rochester, Minn.: I became interested in this problem almost from the beginning, because the Mayo Clinic units were stationed in New Guinea and my colleagues sent specimens and sections back to me. I also received material from others, so that I have had the opportunity of studying about seventy specimens for biopsy, and I have also studied a group of 100 at the Schick General Hospital in Clinton, Iowa, through the courtesy of Col. D. J. Wilson.

In the first material received from New Guinea there was a lichen-planus-like eruption, but associated with it was a tremendous follicular hyperkeratosis simulating the changes seen in lichen pilaris seu spinulosus of Crocker, which is thought to be on a vitamin A deficiency basis. Many of the men had been on C and K rations and had lost a great deal of weight.

In discussions of this disease at meetings of the Chicago Dermatological Society, Dr. Mitchell from the beginning always stood up for causation by quinacrine hydrochloride, and I believe that Dr. Callaway reported a case in the South before the beginning of World War II. I am now convinced that quinacrine hydrochloride is the main cause of this atypical lichen planus, even though the predominance of the cases came from New Guinea, though later reports of some cases were made from the Italian, Mediterranean and other theaters of war.

When dermatitis from arsphenamine was first reported, there were several cases of lichenoid eruption, clinically and histologically, that occurred from this drug, and lichen-planus-like eruption is also seen in association with dermatitis from gold and other heavy metals and also other dermatoses such as disseminate lupus erythematosus and even lymphoblastoma.

In some cases of "New Guinea lichen planus," the cutaneous manifestations were relatively mild and the systemic manifestations severe, as was the case of a chaplain who had not lost weight and who had mild cutaneous symptoms but died of aplastic anemia. Other blood dyscrasias and cirrhosis have been reported.

In answer to Dr. Sulzberger, in "New Guinea lichen planus" there is definite liquefaction degeneration of the basal cell layer, extending down to the base of the hair follicles. The inflammatory reaction in the cutis is greater than that seen in vitamin A deficiency states. I did not find that the sweat ducts were especially affected in the early cases of "New Guinea lichen planus" in which there was considerable loss of weight and in which there was plugging of the external portions of the hair follicles.

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R. G. Senour, President, 937 Carew Tower, Cincinnati 2.  
Alfred L. Weiner, Secretary-Treasurer, 615 Union Central Bldg., Cincinnati 2.  
Place: Cincinnati. Time: 8:15 p. m., first Wednesday of each month, except  
July, August and September.

DR. JAMES H. MITCHELL, Chicago: I want to thank Dr. Montgomiery for coming to my defense, because I took a beating for a while. Just for the sake of the record, I should like to review a few of the episodes in this affair, going back to February 1944. I discussed this at the last meeting of this association in Chicago. Dr. Caro presented a man and wife with lichen planus, making an interesting situation. Dr. Fred Schmidt and I, in talking with the patients, found that they had been taking quinine over the years and that, in the absence of a further supply, had begun to take quinacrine hydrochloride.

In the following two weeks I saw in the office on the same day a private corpsman and a major who were in the same outfit but had not met each other. Biopsies were made in both cases. The private was presented at a meeting of the Chicago Dermatological Society. The sections and pictures of both were presented. These men were kept under observation, and the major is still under observation.

Following this, Dr. Senear and I made a number of trips, the first trip being to Vaughn Hospital, at which time we saw some 55 patients who had just been shipped in. The conditions were all assumed to be due to fungous infection. I called attention to the fact that if one wanted to get rid of ringworm of the feet, one should go to New Guinea and get a quinacrine hydrochloride eruption, because patients with this condition were free from any manifestation, which reminded me that Dr. Pardo-Castello two years ago said that the Cubans who go barefoot do not have ringworm of the feet.

At the meeting in December 1944, 9 of these patients were presented at the Chicago Dermatological Society. The histories were withdrawn, and although the cases were discussed they were not to be published. Later, Dr. Senear and I got preemptory letters from Lieutenant Colonel Wilson, calling our attention to the fact that we probably would suffer dire consequences if we gave out any information. However, I did continue to talk about the situation and showed pictures at various meetings at the various military hospitals. I still feel that we are dealing with something interesting here.

I saw 3 patients in the Medical Corps of the Presbyterian Hospital Unit, in which attention was called to the fact by Dr. Alden that the eruption was commoner among physicians. Another observation that I should like to make is that 1 man who is still under observation, a corpsman in the Presbyterian Unit, who had the most extensive involvement of any person I saw, had, instead of anhidrosis, the most excessive hyperhidrosis I have ever seen in any person. This has since cleared up, but during last summer he said that it was impossible to go about in ordinary society. His clothes were wringing wet when he came in. I am interested to know whether such hyperhidrosis has been observed in other cases.

DR. DONALD M. PILLSBURY, Philadelphia: My opportunity for observation of the quinacrine hydrochloride syndrome was during a thirty day tour of duty in various Army hospitals in the United States in November 1944. There were no such cases in the European Theater. There were a great many persons in the European Theater of Operations who had severe avitaminosis, having been prisoners of war and having lost 70 to 80 pounds (31.8 to 36.3 Kg.) of weight, but I saw no instances of anything similar to the quinacrine hydrochloride syndrome in such patients. In several thousand dermatologic patients seen in the North African Theater, I am sure that I did not observe any instances of the exaggerated form of the disease, though there is no question but that a few such cases were observed in dermatologic centers in the British army.

Conditions as to heat, though possibly not as to moisture, were similar in the summer season in the North African Theater to those which were encountered,

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## CHEMOSURGICAL TREATMENT OF CANCER OF THE FACE

A Microscopically Controlled Method of Excision

FREDERIC E. MOHS, M.D.

MADISON, WIS.

THE DEVELOPMENT of the chemosurgical method has been described,<sup>1</sup> as has the use of the method in the treatment of cancer in specific sites such as lip,<sup>2</sup> nose,<sup>3</sup> ear<sup>4</sup> and eyelid.<sup>5</sup> This article concerns the chemosurgical treatment of cancer of the face, exclusive of the nose, ear, eyelid and vermillion portion of the lips.

### TECHNIC

The most important feature of the chemosurgical treatment of cancer is the microscopic control of excision afforded by the technic hereinafter described.

As the term "chemosurgery" suggests, the tissues are chemically treated and then surgically excised. The chemical treatment serves to produce fixation of the tissues, so that specimens may be excised for systematic microscopic examination.

To illustrate the technic there will be described the chemosurgical treatment of a simple squamous cell epithelioma of the temple (fig. 1A).

This paper is part of a guest lecture at the Cleveland Meeting of the American Academy of Dermatology and Syphilology on Dec. 11, 1946.

This project was aided by the Thomas E. Brittingham Fund, the Wisconsin Alumni Research Foundation and the Jonathan Bowman Memorial Fund.

From the Department of Surgery, Dr. E. R. Schmidt, chief, Wisconsin General Hospital, and the McArdle Memorial Laboratory for Cancer Research, University of Wisconsin School of Medicine.

1. (a) Mohs, F. E., and Guyer, M. F.: Pre-Excisional Fixation of Tissues in the Treatment of Cancer in Rats, *Cancer Research* **1**:49 (Jan.) 1941. (b) Mohs, F. E.: Chemosurgery: A Microscopically Controlled Method of Cancer Excision, *Arch. Surg.* **42**:279 (Feb.) 1941.

2. Mohs, F. E.: Chemosurgical Treatment of Cancer of the Lip: A Microscopically Controlled Method of Excision, *Arch. Surg.* **48**:478 (June) 1944.

3. Mohs, F. E.: Chemosurgical Treatment of Cancer of the Nose: A Microscopically Controlled Method of Excision, *Arch. Surg.* **53**:327 (Sept.) 1946.

4. Mohs, F. E.: Chemosurgical Treatment of Cancer of the Ear: A Microscopically Controlled Method of Excision, *Surgery* **21**:605 (May) 1947.

5. Mohs, F. E.: Chemosurgical Treatment of Cancer of the Eyelid: A Microscopically Controlled Method of Excision, *Arch. Ophth.*, to be published.

in the Southwest Pacific. One big difference, however, was that the period of ingestion of quinacrine hydrochloride was not as long. It was ordinarily from November to March, and then the use of the drugs was discontinued. Sometimes the period of administration of quinacrine hydrochloride was shorter than that, and the discipline with administration of the drug was not so strict as that in troops in the Southwest Pacific.

There have been patients seen, as has been mentioned, with aplastic anemia apparently due to quinacrine hydrochloride. I saw the section of the liver of a medical corps officer in Letterman General Hospital who had atypical lichen planus and whose hepatic disease was also considered to be due to quinacrine hydrochloride.

There are many factors concerned—including an unknown factor, if you will. There may be vitamin factors. There certainly are factors of dermatophytosis, pyogenic infection, photosensitivity and contact dermatitis in precipitating the eruption, but I should certainly vote for the fact that quinacrine hydrochloride is the essential factor in the disease. It seems to me that the evidence on this point is inescapable.

DR. HERBERT S. ALDEN, Atlanta, Ga.: I am glad that this little talk engendered so much discussion. It is obvious that physicians who experienced this cutaneous disease in the Army had a much severer type of eruption to deal with than did physicians in the Navy. It was just that point that I wished to bring out. The disease being discussed as atypical lichenoid dermatitis is, I believe, a much milder form of eruption due to quinacrine hydrochloride, more of a fixed type, while the other type is acute and more severe.

In regard to Dr. Sulzberger's remarks about anhidrosis I hardly think that I can agree that it was a factor in the patients I saw. While it can be said that the ones with generalized follicular involvement were dry and did not sweat, I can recall vividly 7 patients of whom we tried to get photographs in a hot little room in a hospital, and they were sweating so thoroughly that we had difficulty arranging the lights to get a good photograph.

Regarding the vitamin deficiencies in this disease, physicians in the Navy certainly did not encounter such. The patients whom I saw in the Army were unhappy, they did not eat and they were thin, but I am sure that I never saw dermal evidence of vitamin deficiency among them. I admit that they did not like C rations, but I do not think that they went so far as to have any severe vitamin deficiencies. Hence, I do not believe, from my observations, that dietary deficiencies were even a minor factor in the production of these eruptions. I do think that emotional difficulties, fear and unhappiness, as sometimes appears in cases of lichen planus, had something to do with the production of atypical lichenoid dermatitis.

Aplastic anemia, as I mentioned, did not occur in our series of cases, and I know that Major Harvey, of the United States Army, who studied some of these patients, did not believe that quinacrine hydrochloride had anything to do with aplastic anemia or hepatic disease. He, incidentally, was unable to find differences in the quinacrine hydrochloride level in the skin in the eruptive areas and that in the normal skin. He found 30.7 Gm. of quinacrine hydrochloride in the average plasma and about half of that amount in the skin, both in the eruptive areas and in the normal skin.

Like Dr. Pillsbury and others, I think that the evidence that quinacrine hydrochloride is a major factor in this eruption is too overwhelming to neglect. But I do not think that it is the only factor. Other factors were wartime difficulties, sweat and heat, and I do not think that those combinations will repeat themselves again. At least, I hope not.

frozen sections were cut through the under surface of each specimen. Scanning of the sections under the microscope revealed two areas of cancer, *a* and *b*, corresponding to downgrowths *a* and *b* in the vertical view (fig. 2A). 6. Further application of the fixative was limited to these two areas. 7. The next day a cancer-free plane was reached (fig. 2C). The wound, which was covered with a thin layer of fixed tissue, was dressed with a cotton dressing spread with petrolatum to avoid drying. 8. One week later the final layer of fixed tissue had loosened, so that it easily was dissected off with sharp-pointed scissors. 9. The granulation tissue (fig. 1B) was covered with scarlet red ointment-impregnated gauze over which a cotton dressing was placed. The wound healed in three weeks with a flat soft smooth scar which, though pink at first, faded to the color of the surrounding skin (fig. 1C).

The average time in which the final layer of fixed tissue separates from living tissue varies for different areas of the face (table 1). There may be individual variation of two or three days above or below these average figures.

TABLE 1.—*Average Time Required for Separation of Final Layer of Fixed Tissue in Various Regions of the Face*

Region	Average Number of Days
Chin.....	5.8
Forehead.....	6.5
Upper lip (skin).....	6.6
Cheek.....	7.2
Neck.....	8.4
Temple.....	8.8
Scalp.....	10.5

Cancerous involvement of periosteum and even of the bone itself may occur, particularly in regions where the skin closely overlies the bone, as on the forehead, scalp, temple and upper part of the cheek. The chemosurgical technic readily may be used to trace out cancer in the periosteum, but, of course, it is not feasible to make frozen sections of the bone itself. Fortunately, bone often bars the deep extension of cancer for a long period, and when involvement of bone does occur the erosion is grossly visible. Chemical fixation of bone is easily accomplished by means of zinc chloride though the penetration is slower than through soft tissues, and instead of the scalpel the tools used are the rongeur and chisel. When there is doubt as to the nature of the tissue causing the honeycombing of the bone, frozen sections may be made of the bits of soft tissue dissected from the bone. The separation of chemically fixed bone requires about three weeks unless it has received roentgen or radium irradiation, in which case separation is delayed.

Cancerous erosion through the skull with involvement of the underlying membranes and brain does not necessarily contraindicate the continuation of chemosurgical treatment unless the diameter of the defect in the skull exceeds 4 cm. or unless a vital area of the brain is involved.

## EFFECTS OF RESIN OF PODOPHYLLUM ON NORMAL SKIN, CONDYLOMATA ACUMINATA AND VERRUCAE VULGARES

MAURICE SULLIVAN, M.D.

BALTIMORE

AND

LESTER S. KING, M.D.

CHICAGO

PODOPHYLLUM consists of the dried rhizome and roots of *Podophyllum peltatum* Linné, the May apple or mandrake, a perennial plant of northern and middle United States.<sup>1</sup> The extract and active principle of podophyllum is a complex mixture of resinous substances known as podophyllin, resina podophylli or resin of podophyllum<sup>2</sup>; it is an amorphous powder varying from light brown to greenish yellow and turning darker when exposed to temperatures exceeding 25 C. or when exposed to light. Resin of podophyllum is soluble in normal solutions of potassium and sodium hydroxide. In alcohol it forms a slightly opalescent and faintly acid solution. Undiluted resin of podophyllum is irritating to mucous membrane, especially that of the eye, where it may produce extensive damage.<sup>3</sup> In the past resin of podophyllum was frequently prescribed, as it is an ingredient of the erstwhile popular and official vegetable cathartic pill the formula for which is compound extract of colocynth 0.06 Gm., extract of hyoscyamus 0.03 Gm., extract of leptandra 0.015 Gm. and resin of podophyllum 0.014 Gm.<sup>2</sup> It was considered to be a secretory and excretory cholagogue.

In 1936 Viehover and Mack<sup>4</sup> conducted a study of the biochemistry of resin of podophyllum. They pointed out the following facts concerning resin of podophyllum: It is a mixture of physiologically active and

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Read at the Sixty-Sixth Annual Meeting of the American Dermatological Association, Hot Springs, Va., June 10, 1946.

From the Skin and Venereal Diseases Section of the Medical Service and the Laboratory Service of the William Beaumont General Hospital, El Paso, Texas.

1. Blumgarten, A. F.: Text Book of *Materia Medica, Pharmacology and Therapeutics*, ed. 7, New York, The Macmillan Company, 1937, pp. 220 and 223.

2. *Pharmacopoeia of the United States*, ed. 11, Easton, Pa., Mack Printing Company, 1936, pp. 294 and 319.

3. (a) Hutchinson, J.: Severe Ulceration of the Cornea Caused by the Dust Given Off by Podophyllin Root Whilst Being Ground, *M. Times & Gaz.* **2**:516, 1872. (b) Chiari, M.: *Podophyllinvergiftung*, *Zentralbl. f. Biochem. Biophysik.* **12**: 557, 1911-1912; *La podofillina causa di disturbi oculari*, *Clin. ocul.* **110**347, 1910.

4. Viehover, A., and Mack, H.: Biochemistry of May Apple Root (*Podophyllum Peltatum*), *J. Am. Pharm. A.* **27**:632, 1938.

Thus, in the three year period successful results were obtained in 100 per cent of the 174 cases in the determinate group.

*End Results After Five Years or More.*—In the group of 137 cases observed for five years or more there were 43 cases in the indeterminate group and 94 cases in the determinate group. In the five year period successful results were obtained in 100 per cent of the 94 cases of the determinate group.

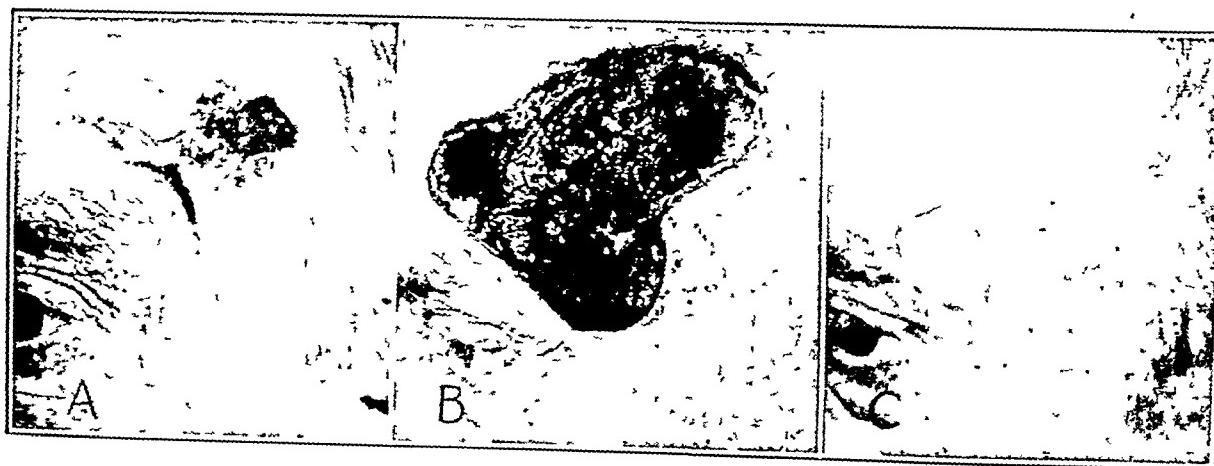


Fig. 3.—*A*, basal cell epithelioma of group D. *B*, granulation tissue after the cancer had been excised in four microscopically controlled stages and after removal of the final layer of fixed tissue. *C*, healed lesion. The patient is free of cancer after three and one-half years.

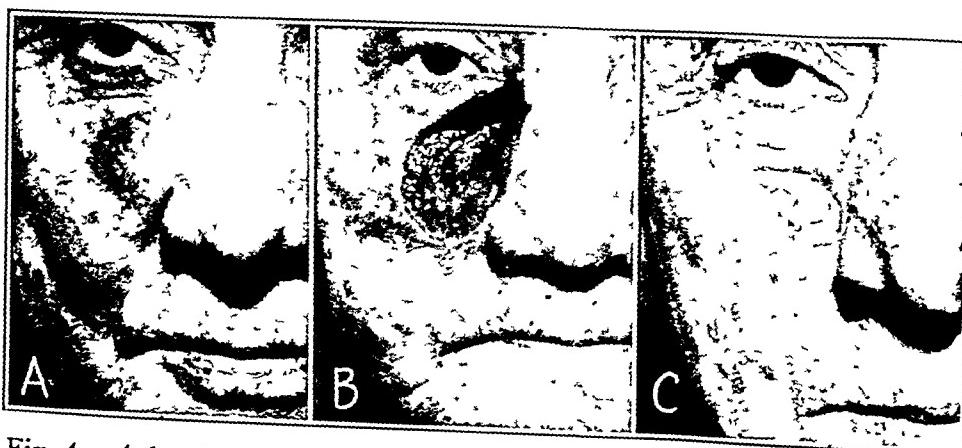


Fig. 4.—*A*, basal cell epithelioma of group C which had recurred after surgical excision seven years before. *B*, granulation tissue after separation of final layer of fixed tissue. The cancer had extended superiorly for an unsuspected distance. *C*, healed lesion. The patient was free of cancer when she died of an accident after over two years.

*Effect of Size of Lesion on Prognosis.*—In the 174 cases in the determinate group in the three year period, the lesions were divided into four groups according to their average diameter as measured at the initial clinical examination: *A*, under 1 cm.; *B*, 1 to 2 cm.; *C*, 2 to 3 cm. (figs. 4 and 6) and *D*, 3 or more cm. (figs. 3 and 5).

inactive substances and contains a predominantly toxic as well as a decidedly laxative substance. Only one active crystallizable substance, occurring as such, has thus far been isolated from resin of podophyllum, namely, podophyllotoxin. Commercial podophyllotoxin is an impure, only partially crystalline substance which exhibits both toxic and laxative properties; the pure crystalline podophyllotoxin exhibits predominantly toxic properties. Need for the revision of the pharmacopoeial method of extraction as well as the official standard for resin of podophyllum was emphasized by Viehover and Mack as the result of their study. They stated: "Two facts are obvious: *First*, that the drug is essentially unfit for human consumption until it can be freed from its highly toxic, irritating principles and subsequent harmful reactions; *second*, that should the drug prove satisfactory, after refinement, for administration, an infallible method for regulating its medicinal use should be established." In the latest, the twelfth edition (1942) of the United States Pharmacopeia, podophyllum is listed under "Articles Official in the U. S. P. XI But Not Admitted to the U. S. P. XII."<sup>5</sup> In spite of its official obsolescence resin of podophyllum is still a frequently used drug, as it is an ingredient of several widely marketed and extensively advertised cathartic pills. Ivy and his co-workers<sup>6</sup> examined critically the claims of one popular brand of cathartic pills containing resin of podophyllum and concluded that in therapeutic doses it "is not a choleric and is neither a cholecystokinetic nor a noncholecystokinetic cholecystogogue."

For many years, according to Kittredge,<sup>7</sup> the urologists in New Orleans have treated genital verrucae with topical applications of resin of podophyllum. This treatment was not generally known until 1942, when Kaplan<sup>8</sup> reported that condyloma acuminatum rapidly and permanently underwent involution after one or two treatments with a 25 per cent suspension of resin of podophyllum in liquid petrolatum. The results in subsequent reports by Kaplan and his co-workers<sup>9</sup> and MacGregor<sup>10</sup>

5. Pharmacopoeia of the United States, ed. 12, Easton, Pa., Mack Printing Company, 1942, p. lxxxvi.

6. Ivy, A. C.; DeHoog, H., and Gutmann, M.: The Effects of Aloes and Podophyllum (Resin) (Carter's Little Liver Pills) on the Output of Bilirubin and Cholic Acid in Canine Duodenal Drainage Fluid, Quart. Bull. Northwestern Univ. M. School **19**:102, 1945.

7. Kittredge, W. E.: Personal communication to the authors.

8. Kaplan, I. W.: Condylomata Acuminata, New Orleans M. & S. J. **94**: 338, 1942.

9. (a) Culp, O. S.; Magid, M. A., and Kaplan, I. W.: Podophyllin Treatment of Condylomata Acuminata, J. Urol. **51**:655, 1944. (b) Culp, O. S., and Kaplan, I. W.: Condylomata Acuminata: Two Hundred Cases Treated with Podophyllin, Ann. Surg. **120**:251, 1944.

While 59 of the lesions were under 1 cm. in average diameter, a much larger number were of larger size (table 2). Inasmuch as all of the lesions, regardless of size, were successfully treated, it may be concluded that the size of the lesion is not an appreciable factor in the determination of prognosis. This is not to imply, however, that all basal cell epitheliomas of the face can be cured by means of the chemosurgical method. Obviously, if a cancer should extensively involve vital structures, such as certain portions of the brain or the internal carotid and jugular vessels, the neoplasm might become incurable despite the microscopic control of the chemosurgical method.

*Effect of Previous Treatment on Prognosis.*—Of the 174 cases in the determinate group in the three year period there were 60 (34.5 per cent) in which the patients had previously received unsuccessful treatment by operation, irradiation or caustics. All the 60 recurrent lesions, as well as the 114 lesions for which the patients had not received previous treatment, were cured by means of chemosurgical treatment.

TABLE 2.—*Distribution of Basal Cell Epithelioma According to Size*

Group	Average Diameter, Cm.	Number of Lesions
A.....	Under 1	59
B.....	1-2	58
C.....	2-3	31
D.....	3 or more	26
All groups.....		174

The high curability of recurrent basal cell epitheliomas of the face by means of chemosurgical excision is in contrast to the low curability of such lesions by other methods.

*Effect of Degree of Malignancy on Prognosis.*—It is convenient to classify basal cell epithelioma into two groups, "invasive" and "non-invasive," to provide a rough indication of the degree of malignancy. The invasive type is characterized by slender, poorly demarcated strands of cancer cells with an indefinite basement membrane between them and the copious connective tissue stroma. The noninvasive type is composed of relatively large, rounded clumps of basal cells, well demarcated by an intact basement membrane from the surrounding sparse connective tissue stroma. Clinically the invasive type tends to show the erosion, ulceration and deep invasion which are characteristic of the rodent ulcer type of basal cell epithelioma (illustrated by figs. 3, 5 and 6), while the noninvasive type tends to show the protruding rounded skin-covered mass characteristic of the nodular type of basal cell epithelioma (illustrated by fig. 4). Of course, intergradations between these two types are frequent.

have justified Kaplan's original enthusiasm for this simple and effective method. Thus far no satisfactory explanation for the curative action of resin of *podophyllum* on condylomata acuminata has been presented. The purpose of this study is to collect data which may aid in the elucidation of the biologic action of resin of *podophyllum*.

#### CLINICAL OBSERVATIONS OF RESIN OF PODOPHYLLUM ON NORMAL SKIN AND MUCOUS MEMBRANE

*A. Normal Skin.*—O'Donovan<sup>11</sup> reported 2 cases of dermatitis due to contact with resin of *podophyllum*. The patients were employed by wholesale manufacturing druggists and were exposed to large quantities of the drug while grinding and sifting it. The early literature was reviewed by O'Donovan,<sup>12</sup> and several other reports of dermatitis due to resin of *podophyllum* were found. In a case report published in 1872 it was noted, "It appears from statements of a patient now under Mr. Hutchinson's care at Moorfields that *podophyllum* dust is known in the trade to produce 'inflamed eyes' and an eruption of 'scabs' on the arms and legs of men who attend the mill in which the root is ground." Webster<sup>12a</sup> in 1877 recorded a case of dermatitis of the face and conjunctivitis in a chemist's assistant who was working with the powdered resin. In 1882 Winterburn<sup>12b</sup> noted an eruption of the scrotum in workers handling *podophyllum*. Rubefacient and vesicant effects due to accidental contamination of the skin of his arm with an alcoholic solution of resin of *podophyllum* were remarked by Bentley.<sup>12c</sup> The following quotation from a manufacturer's letter was included in Bentley's communication:

It has one property I have not seen mentioned, viz. that of causing soreness and little pustules in the nose and inflammation of the eyelids when any particles of the 'podophyllin' powder are allowed to remain many minutes in contact with the skin of those parts; so much so, that five persons employed in its preparation and in putting it into bottles were all affected in the manner described. We are now very careful not to inhale any of the dust, but keep the mouth and nostrils covered with fine muslin or handkerchiefs, whilst engaged in handling or preparing it.

Viehoever and Mack<sup>4</sup> mentioned inflammation of the skin of the face of a student who was working with extracts of resin of *podophyllum*.

In order to study the effects of 25 per cent resin of *podophyllum* in oil on normal skin, patch tests with 25 per cent resin of *podophyllum*

10. MacGregor, J. V.: Treatment of Soft Warts with Podophyllin, Brit. M. J. 1:593, 1945.

11. O'Donovan, W. J.: Dermatitis Due to Podophyllin Resin, Brit. J. Dermat. 47:13, 1935.

12. (a) Webster, D.: A Case of Poisoning by Contact of the Powder of Resin of Podophyllin, M. Rec. 12:357, 1877. (b) Winterburn, G. A.: Louisville M. News 8:187, 1882. (c) Bentley, R.: Pharm. J. 3:462, 1861; cited by O'Donovan.<sup>11</sup>

The primary lesion was eradicated in 68 of the 70 cases in the determinate group in the three year period (97.1 per cent). Most of the failures were due to the presence of uncontrolled regional metastases.

*End Results After Five Years or More.*—There were 50 cases of squamous cell epithelioma observed for five years or more. Of these cases 22 were in the indeterminate group and 28 were in the determinate group. Successful results were obtained in 82.1 per cent of the cases in the determinate group.



Fig. 7.—A, squamous cell epitheliomas of groups A, B and C. B, healed lesions. The patient is free of cancer after over six years.

*Effect of Size of Lesion on Prognosis.*—The squamous cell epitheliomas were divided into four groups according to size as measured at the initial clinical examination: A, under 1 cm. in average diameter (fig. 7); B, 1 to 2 cm. (figs. 7 and 8); C, 2 to 3 cm. (fig. 7) and D, over 3 cm. (fig. 9). All of the 52 lesions in groups A, B and C were successfully treated, but of the 18 lesions in group D only 7, or 38.8 per cent, were

in liquid petrolatum were applied to the volar aspects of the forearms of 200 men. The drug was in contact with the skin for twenty-four hours in 100 cases and for forty-eight hours in the other 100. Approximately

TABLE 1.—*Results of 200 Patch Tests with 25 Per Cent Resin of Podophyllum in Oil*

Hours of Contact with the Skin	Number of Tests	Positive Reactions, per Cent
24	100	30
48	100	69

0.1 to 0.2 cc. of the suspension was used for each test. Thirty per cent of the twenty-four hour tests elicited positive reactions. Sixty-nine per cent of the forty-eight hour tests elicited positive reactions (table 1).

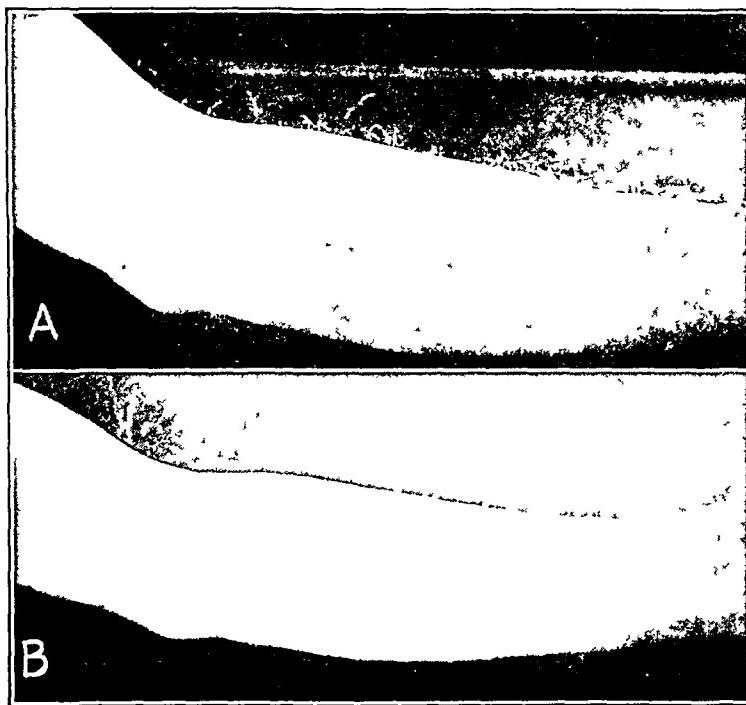


Fig. 1.—A, severe positive reaction to a patch test of 25 per cent resin of podophyllum in liquid petrolatum applied for forty-eight hours, manifested by erythema almost hemorrhagic in intensity and edema. No vesiculation or ulceration occurred in such reactions. B, postinflammatory pigmentation at the site of the reaction in A six days later. This faded gradually, and it disappeared entirely in one month.

The degree of positive reaction ranged from the earliest manifestation of a few erythematous macules to extensive pruritic, intensely erythematous and edematous plaques with peripheral broad pseudopodia. In some of the severe reactions the erythema was almost hemorrhagic in intensity. No vesiculation or ulceration occurred. In all cases the reactions subsided in four to seven days. In the severe type there was some residual postinflammatory pigmentation, which subsided in several

*Effect of Previous Treatment on Prognosis.*—Of the 70 squamous cell epitheliomas in the determinate group, 19 (27.1 per cent) had recurred after previous unsuccessful surgical or radiation therapy. The prognosis for previously treated lesions was distinctly poorer than for the previously untreated lesions. Of the 19 previously treated lesions 11 (57.9 per cent) were successfully treated by the chemosurgical method, while of the 51 previously untreated lesions 48 (94.1 per cent) were successfully treated. The poorer prognosis in the group which had previously been treated was not due so much to the effects of the previous treatment *per se* as it was to the delay which allowed complications such as metastasis and excessively widespread local involvement to occur.

*Effect of Histologic Grade of Malignancy on Prognosis.*—Classification of the 70 squamous cell epitheliomas of the determinate group according to Broder's four grades of malignancy revealed a strong correlation between histologic structure and prognosis (table 4). The greater tendency for early metastasis and for deep invasion into vital

TABLE 4.—*Effect of Histologic Grade of Malignancy of Squamous Cell Epithelioma on Prognosis*

Grade	Number of Lesions	Successful Results	
		Number	Percentage
1.....	18	17	94.4
2.....	31	28	90.3
3.....	19	14	73.7
4.....	2	0	0

structures associated with the more highly malignant lesions is responsible for the poorer prognosis. However, a highly malignant epithelioma in which these complications have not occurred is just as readily cured by chemosurgical treatment as one of lower malignancy.

*Effect of Site of Cancer on Prognosis.*—While there was considerable variation in the proportion of successful results in various sites, not much significance can be attached to the results because of the relatively few cases in some of the groups (table 5). All the unsuccessful results were due to uncontrolled metastasis with exception of 1 lesion of the temple with excessive involvement of the soft tissues and bone and 1 lesion on the chin with excessive involvement of the mandible and larynx.

*Effect of Metastasis on Prognosis.*—By far the most important single adverse influence on prognosis in this series of squamous cell epitheliomas of the face was the presence of metastasis. Thus, while none of the 9 patients with metastasis were cured, 96.7 per cent of the patients without metastasis were successfully treated.

The primary lesion was successfully treated in all the 9 patients for whom results are listed as unsuccessful because of uncontrolled metas-

weeks. Forty-five subjects were retested at other sites on the same forearm or on the opposite forearm one, two or three months later (table 2). The original tests in 22 of the subjects gave positive reactions; all elicited positive reactions subsequently. The reactions in ten of the subsequent tests were severer than the original reactions. In 4 of the

• TABLE 2.—*Results of Retesting 45 Subjects with 25 Per Cent Resin of Podophyllum in Oil, One, Two or Three Months Later*

Result of Original Test	Number Retested	Results of Subsequent Tests
Positive	22	Positive in 22 (or 100%) In 10 the reaction was severer than the original reaction In 4 there was reactivation of previous tests at other sites
Negative	23	Negative in 18 (or 78.26%) and positive in 5 (or 21.74%)

22 patients plaques of erythema and edema appeared at other sites where patch tests had been applied previously. In 23 of the subjects the first reactions were negative; on retesting, in 18 the results were negative and in 5 they were positive. The high percentage of positive reactions, the increasing severity of the reactions to repeated tests, the reactivation of previous tests at other sites and the positive reactions which developed after repeated applications in subjects who had previously not reacted are evidence that resin of podophyllum is a sensitizer of the first order.

*B. Mucous Membrane.*—To the under surfaces of the prepuces of 6 men scheduled for circumcision resin of podophyllum in oil was applied. The applications were made twenty-four and forty-eight hours before the operations. Various degrees of mucositis and balanitis resulted in each case.

#### CLINICAL OBSERVATIONS OF CONDYLOMATA ACUMINATA TREATED WITH 25 PER CENT OF PODOPHYLLUM IN OIL

Fifty patients were treated according to the technic recommended by Kaplan.<sup>8</sup> In 48 of the patients the verrucae involved the penis. One hundred per cent were cured after one or two applications. In 2 patients, 1 man and 1 woman, the condylomas were perianal and of long duration. These underwent partial involution but were not cured.

Our observations of the clinical effects were similar in important details to those described by Kaplan,<sup>8</sup> Culp and Kaplan<sup>9b</sup> and Culp, Magid and Kaplan.<sup>9a</sup> The main difference was that in all the patients treated by us there was inflammation of the adjacent normal mucous membrane, whereas Kaplan and his co-workers emphasized the lack of effect on the surrounding normal tissue.<sup>9</sup> The applications were pain-

Ninety-six of the lesions were senile keratoses, 36 were seborrheic keratoses, 26 were so-called squamous cell papillomas and 6 were cutaneous horns.

The procedure used depends on the clinical appearance. If the keratosis appears "inactive," that is, if it shows little evidence of proliferation in its base, it is often sufficient to cut or scrape off the keratin and cauterize the base with dichloroacetic acid. This procedure is also sufficient for the usual case of seborrheic keratosis.

However, if the keratosis shows evidence of becoming "active," as indicated by proliferation of the epithelium at the base, by induration or ulceration, it is safer to excise chemosurgically a layer for microscopic examination. This procedure eliminates the danger of failing to diagnose and treat adequately an early epithelioma.

#### COMMENT

The reliability of the chemosurgical method is indicated by the fact that in the determinate groups in the three year period 100 per cent of the 174 basal cell epitheliomas were successfully treated, while 84.3 per cent of the squamous cell epitheliomas were cured.

The best series reported in the literature, not only from the standpoint of excellence of results, but also from the standpoint of statistical validity, is that of Magnussen.<sup>8</sup> He reported the results obtained in the treatment of epithelioma of the face with the advanced radiologic, surgical and electrosurgical technics employed at *Radiumhemmet* in Stockholm, Sweden. From his protocols it was determined that in the three year period successful results were attained in 95.2 per cent of the 169 cases of basal cell epithelioma of the face in the determinate group. For squamous cell epithelioma successful results were attained in 76.2 per cent of 42 cases.

The results of chemosurgical treatment compared favorably with the results of Magnussen. Thus, for the basal cell epithelioma the rate of cure in the present series was 100 per cent as compared with 95.2 per cent in Magnussen's series. This record was attained in spite of a greater proportion of large lesions (32.8 per cent were in groups C and D, as compared with 28.3 per cent in Magnussen's series) and in spite of a greater proportion of recurrent lesions (34.5 per cent as compared with 32.8 per cent in Magnussen's series). Similarly, for squamous cell epithelioma the rate of cure in the present series was 84.3 per cent as compared with 76.2 per cent in Magnussen's series in spite of the greater proportion of large lesions (40 per cent in groups C and D as compared with 27.5 per cent in his series) and in spite of the greater

8. Magnussen, A. H. W.: Skin Cancer: A Clinical Study with Special Reference to Radium Treatment, *Acta radiol.*, 1935, supp. 22, p. 1.

less and were made with ordinary cotton-tipped wood applicators. It soon became apparent that it was not possible in every case to confine the oily material to the verrucae. Some of it invariably spilled on the adjacent mucous membrane or was transferred by contact to the overlying foreskin. As we had found that contact of the suspension with



Fig. 2.—*A*, condylomata acuminata on the glans penis and in the coronal sulcus before treatment with 25 per cent resin of podophyllum in oil. *B*, six days after treatment. Note the areas of inflammation peripheral to the sites of the treated verrucae. This represents a mild amount of irritation to the adjacent normal mucous membrane.

mucous membrane for more than twenty-four hours resulted in inflammation, an attempt was made to devise means for avoiding contact as much as possible with the adjacent mucous membrane. This was accomplished partially by wiping away with a dry applicator any excess material after the verrucae had been thoroughly covered. In some cases

## ADENOACANTHOMA OF SWEAT GLANDS

Carcinoma of Sweat Glands with Glandular and Epidermal Elements;  
Report of Four Cases

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THE HISTOLOGIC appearance of carcinomas of the sweat glands has been reviewed in two recent articles written by Loos<sup>1</sup> and by Gates, Warren and Warvi.<sup>2</sup> The number of cases in the literature accepted by these authors as instances of carcinoma of sweat glands is small. Loos, in 1936, enumerated 28 cases and added 1 of his own; Gates, Warren and Warvi, in 1943, enumerated 30 cases and added 6 personally observed cases. Five of the tumors regarded by Loos as carcinomas of sweat glands were not accepted by Gates, Warren and Warvi. The latter authors stated that even among the tumors which they accepted several did not entirely qualify as carcinomas of sweat glands and might have been either adenoid basal cell epitheliomas or hidradenomas.

Carcinomas of the sweat glands do not possess a characteristic appearance. This makes their recognition and their distinction from other cutaneous tumors often difficult. Loos has suggested classification of carcinomas of sweat glands by dividing them into alveolar, tubular, cystic-papillary and solid forms. He pointed out that combinations of these forms were frequent. Although he took cognizance of the fact that "metaplastic cellular changes in the direction of spinocellular, cornifying proliferations" had been described in several cases, he did not group such tumors as a separate form of carcinoma of the sweat glands.

The histologic appearance of carcinomas of sweat glands in 4 patients studied at the Massachusetts General Hospital is herein described. The interesting feature of these tumors is the presence of squamous and keratinized cells in addition to glandular cells.

### REVIEW OF THE LITERATURE

In 8 of the 41 cases of carcinoma of sweat glands regarded as such by either Loos or Gates, Warren and Warvi the carcinoma contained

From the Departments of Dermatology and Pathology, Massachusetts General Hospital.

1. Loos, H. O.: Die Carcinome der Anhangsgebilde der Haut, Arch. f. Dermat. u. Syph. **174**:465, 1936.
2. Gates, O.; Warren, S., and Warvi, W. N.: Tumors of Sweat Glands, Am. J. Path. **19**:591, 1943.

small cloth patterns were fitted snugly around the bases of single verrucae to protect the mucous membrane. In other cases of multiple verrucae in the coronal sulcus some measure of protection of the overlying foreskin was afforded by placing strips of gauze between the treated area and the foreskin. The end of the gauze was allowed to hang out of the preputial orifice in order to facilitate removal if necessary. In spite of the greatest care in application and the protection of the gauze it was not possible to avoid some irritation to the mucous membrane when the oil suspension was used (fig. 2). It was also observed that unless the foreskin and glans were thoroughly washed twenty-four hours after treatment there was always irritation of the surrounding tissues. The manifestations of the effects on the mucous membrane varied from a peripheral halo of erythema surrounding a single treated verruca to extensive erythema, edema and ulceration. Balanitis and phimosis resulted occasionally in men with long tight foreskins. In some cases, the foreskin could not be retracted for several days and a thick purulent exudate collected in the preputial sac. It was not necessary to perform a dorsal slit or circumcision in these patients. The preputial sac was cleansed daily with a mixture of equal parts of hydrogen peroxide and water. When the balanitis subsided and the foreskin was retracted in such cases, the verrucae had disappeared and on the glans penis and mucous membrane of the foreskin there were well demarcated superficial ulcers covered with or surrounded by blanched macerated tissue. The ulcers healed usually without scar formation.

Clinical effects of treatment of the condylomata acuminata appeared within four to eight hours. The first manifestation was blanching; later there was a drying effect, and the tumors, which previous to treatment had been pink or red and moist, appeared white or gray and dry. In a few cases there were small areas of dark brown or black discoloration on the surface of the treated lesions. In four to twenty-four hours the verrucae decreased in size, and in many cases complete involution occurred within forty-eight hours. The disappearing masses were soft and macerated. In most cases no ulceration could be detected at the healed site. When ulcers resulted they were superficial and healed rapidly (fig. 3).

When it became apparent that contact with normal mucosa for more than twenty-four hours was undesirable, the patients were instructed to wash thoroughly, sometime before twenty-four hours, but not until after eight hours had elapsed, when clinical changes in the verrucae were expected to occur. As an average time, twelve hours was selected as a period during which the drug would be likely to exert its effect and not cause excessive irritation to the adjacent tissue.

they were papillary hidradenomas rather than carcinomas. Both tumors showed in a few areas horn pearls surrounded by squamous cells.

Ricker and Schwalb<sup>8</sup> and Dusseldorp<sup>9</sup> each described a tumor located in the right upper eyelid. The 2 tumors were of small size and had been present for six and seven years, respectively. Histologically, they were encapsulated epithelial tumors containing glandular lumens. Both tumors showed areas in which cells with intercellular bridges and horn pearls were present.

In contrast to the aforementioned 7 tumors in which cornification was either absent or present only to a slight degree, the tumor reported by Deichstetter<sup>10</sup> showed considerable cornification. It is the only tumor which resembles the 4 tumors observed at the Massachusetts General Hospital. The patient, aged 65, had had a traumatic ulcer on his left arm for sixteen years. During the last year the ulcer had grown to a size of 8 by 11 cm. The regional lymph nodes were not enlarged. The ulcer was excised. Histologic examination revealed in the corium numerous large "alveoli" filled with large bright flat epithelial cells resembling squamous cells. In some areas within the alveoli the cells were concentrically layered, the innermost layers of epithelium being keratinized. Thus, rather numerous horn pearls were present in the alveoli. In addition, the tumor showed small narrow intertwining strands of epithelial cells. Numerous sweat glands were present beneath the tumor. Some were normal, others showed cystic dilatation of their lumens and still others showed active proliferation of their epithelium with penetration through the membrana propria of the glands. Deichstetter concluded that the origin of the carcinoma was from sweat glands and that the squamous and keratotic cells in the alveoli had developed by metaplasia from glandular cells. He pointed out the analogy to the simultaneous occurrence of adenocarcinoma and squamous cell carcinoma in the corpus uteri and quoted Emanuel's statement<sup>11</sup> that this may be explained by metaplasia of glandular cells into squamous cells rather than by the simultaneous presence of two carcinomas.

#### REPORT OF CASES

CASE 1.—A 65 year old man was admitted to the Massachusetts General Hospital in January 1942 because of a tumor on his right temple which he had first

8. Ricker, G., and Schwalb, J.: Die Geschwülste der Hautdrüsen, Berlin, S. Karger, 1914, p. 199.

9. Dusseldorp, M.: Adenocarcinoma de glándula de Moll, Rev. de especialid. 4:999, 1929.

10. Deichstetter, H.: Ueber einen Fall von primärem Schweißdrüsencarcinom, Inaug. Dissert., Munich, C. Wolf & Sohn, 1902.

11. Emanuel, R.: Ueber gleichzeitiges Vorkommen von Drüsenkrebs und Hornkrebs im Uteruskörper, zugleich ein Beitrag zur Histogenese der primären Hornkrebs, Ztschr. f. Geburtsh. u. Gynäk. 46:434, 1901.

THE EFFECT OF 25 PER CENT RESIN OF PODOPHYLLUM IN  
OIL ON VERRUCAE VULGARES

One hundred ordinary verrucae in various locations were treated. In 1 patient the warts were on the glans penis and on the shaft of the penis. None responded.



Fig. 3.—*A*, two intraurethral condylomata acuminata. *B*, result four days after single application of 25 per cent resin of podophyllum in oil. Only a minimal amount of irritation to the glans resulted.

These clinical observations suggested that vehicles other than liquid petrolatum should be investigated in an effort to find one which would not have the spreading effect of liquid petrolatum and which would be

of the alveolar formations into their lumens. The projections consisted either of clusters of epithelial cells or of long narrow strands of connective tissue lined with usually a single layer of epithelial cells. Most of the epithelial cells lining the alveolar spaces were cubic or cylindric in shape and did not possess inter-cellular prickles. They appeared to be glandular cells. However, in areas where several layers of epithelial cells were present, the cells of the upper layers had an irregular shape and prickles were noted between them (fig. 3). The lumens contained desquamated epithelial cells. Most of these cells had undergone keratinization. Their cytoplasm had a homogeneous glistening appearance and showed either eosinophilic or, in the most completely keratinized cells, basophilic staining. Some of the cells appeared shrunken, and others were swollen to twice the size of the epithelial cells lining the cysts.



Fig. 2 (case 1).—The epidermis shows atypical proliferations consistent with squamous cell epithelioma. They contain ductlike lumens (sweat ducts) filled partially or entirely with cornified cells. Large alveolar spaces lined by glandular epithelium are connected with the epidermis.

Within the broad band of granulation tissue, scattered islands of epithelial cells were present (figs. 1 and 4). In some islands the epithelial cells lay irregularly, and in others they were in part arranged in strands or around small lumens. A few of the islands contained large central cystic lumens loosely filled with desquamated cells in various stages of keratinization. The majority of the cells composing the islands had the appearance of glandular cells. However, in areas in which the cells were arranged in several layers, some of the cells showed inter-cellular bridges and thus had the appearance of squamous cells.

Underneath the cysts and between the epithelial islands groups of small tubular glands were present (fig. 1, right lower corner). Some appeared to be

more penetrating. The irritation of the adjacent normal mucous membrane is an objectionable feature of this otherwise excellent method, and it cannot be prevented when liquid petrolatum is used. The failures in the cases of the 2 patients with chronic perianal condylomas and the failures in all the cases of verrucae vulgares indicated that penetration may have been prevented by the keratinized surfaces of the verrucae. The perianal condylomas were dry and approximated verrucae vulgares in clinical and microscopic appearance. Aquaphor, petrolatum and "emulsion base number one"<sup>13</sup> were used as vehicles and found to have no particular advantages over liquid petrolatum. Solutions in sodium and potassium hydroxide were inert when applied to condylomata acuminata. It is known<sup>4</sup> that podophyllotoxin is easily susceptible to alkaline hydrolysis. Podophyllotoxin, therefore, may be the substance in resin of podophyllum which is responsible for its effect on condylomata acuminata. Solutions in alcohol proved to be effective, so it was decided to treat another group of patients with condylomata acuminata and another group with verrucae vulgares by applications of 20 per cent resin of podophyllum in 95 per cent alcohol.

CLINICAL EFFECTS OF THE APPLICATION OF A SOLUTION OF 20 PER  
CENT RESIN OF PODOPHYLLUM IN 95 PER CENT ALCOHOL  
TO CONDYLOMATA ACUMINATA AND VERRUCAE  
VULGARES

A. Thirty patients with condylomata acuminata were treated. The condylomas were on the penis in 29 of the patients and were perianal in 1 patient. The applications were painless or nearly painless. By careful application it was possible to confine the solution to the condylomas. Cures resulted in 100 per cent of the group treated. There was considerably less irritation of the normal mucous membrane, although it was not always possible entirely to avoid it (fig. 4).

B. One hundred verrucae vulgares were treated. Included in the group was the patient with the cornified dry verrucae on the penis who had previously been treated unsuccessfully with resin of podophyllum in oil. His warts and the warts in 14 other patients underwent involution after three or four applications of the alcoholic solution. It is realized that 15 per cent of cures of verrucae vulgares is not an impressive percentage of cures for warts, but it indicates that a more penetrating type of vehicle containing resin of podophyllum or podophyllotoxin may be evolved eventually which will provide a satisfactory topical treatment for verrucae vulgares.

13. Pillsbury, D.; Sulzberger, M., and Livingood, C.: Manual of Dermatology, Military Medical Manuals, Division of Medical Science, Committee on Medicine, National Research Council, Philadelphia, W. B. Saunders Company, 1942, p. 379.

normal eccrine sweat glands or sweat ducts, and others differed from normal sweat glands by showing larger lumens into which papillary tufts protruded. Some of the lumens contained desquamated cells. The sweat glands with epithelial proliferations approached in appearance the glandular structures belonging to the tumor.



Fig. 4 (case 1).—An island of tumor tissue is shown in which the central cystic lumen is lined at the left by glandular and at the right by squamous cells.

CASE 2.—A 79 year old man was seen on several occasions between May 1941 and July 1942 because of senile keratoses on his right ear. They were destroyed by electrodesiccation. In February 1943 the patient returned because of a new

The manner in which condylomata acuminata undergo involution after treatment with resin of podophyllum is remarkable to behold. Large as well as small masses of verrucous tissue disappear with dramatic rapidity. In attempting to explain the action of resin of podophyllum on condylomas, Culp and Kaplan<sup>9b</sup> stated, "The most logical assumption is that the irritating power of the drug produces spasm of the small vessels, which in turn produces ischemia, necrosis and sloughing. The blood supply . . . apparently is more susceptible to the 25 per cent suspension than that of the more viable, adjoining, normal tissues." Their assumption was not documented by microscopic observations.

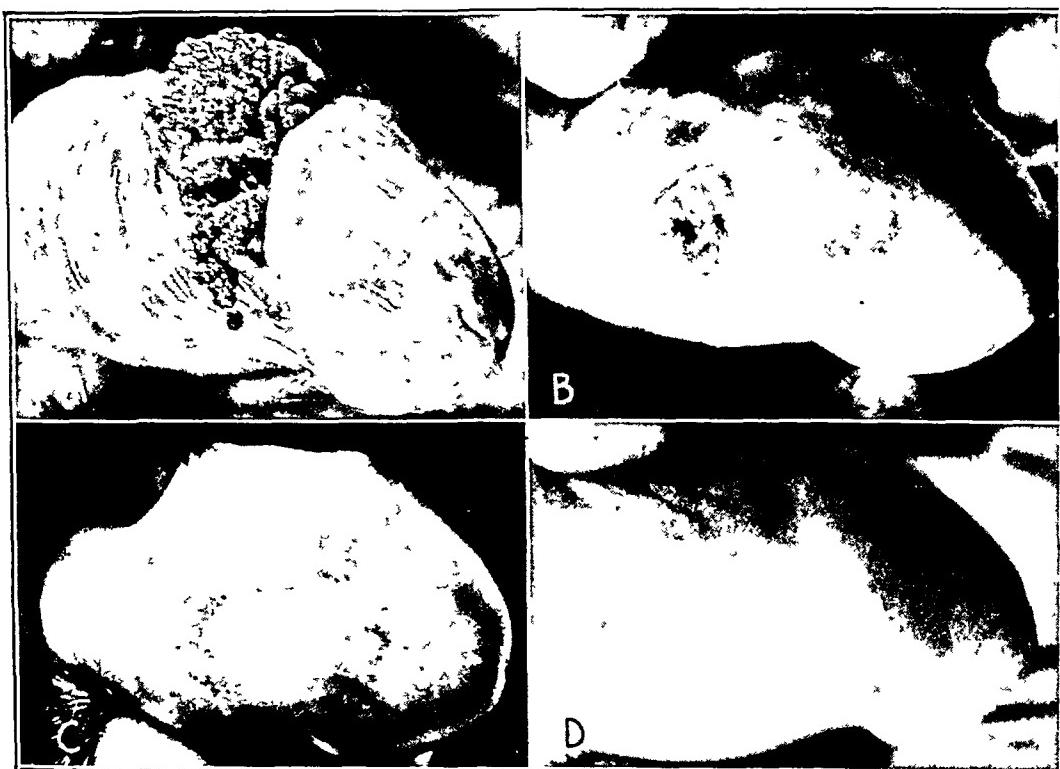


Fig. 4.—*A*, condylomata acuminata in the coronal sulcus. *B*, one week after one application of 20 per cent resin of podophyllum in 95 per cent alcohol. Note the lack of inflammation to the adjacent mucosa due to property of alcoholic solution to remain localized to lesion if precisely applied. *C*, the result one week after a second application of the alcoholic solution. *D*, final result, two weeks later.

#### HISTOLOGIC DATA

In order to provide material for the study of the microscopic changes in normal skin and mucous membranes, six biopsy sections were taken during various states of the positive reactions produced by patch tests, and the six prepuces treated twenty-four and forty-eight hours before circumcision were sectioned and examined. In the prickle layer, the intercellular bridges had disappeared and the cell membranes were thickened and hyalinized. Some of the superficial cells contained a few

CASE 3.—A 77 year old man had been seen intermittently since 1934 because of senile keratoses which developed on various parts of his face. In 1938 a basal cell epithelioma appeared in the nasolabial fold and was treated with radium. In

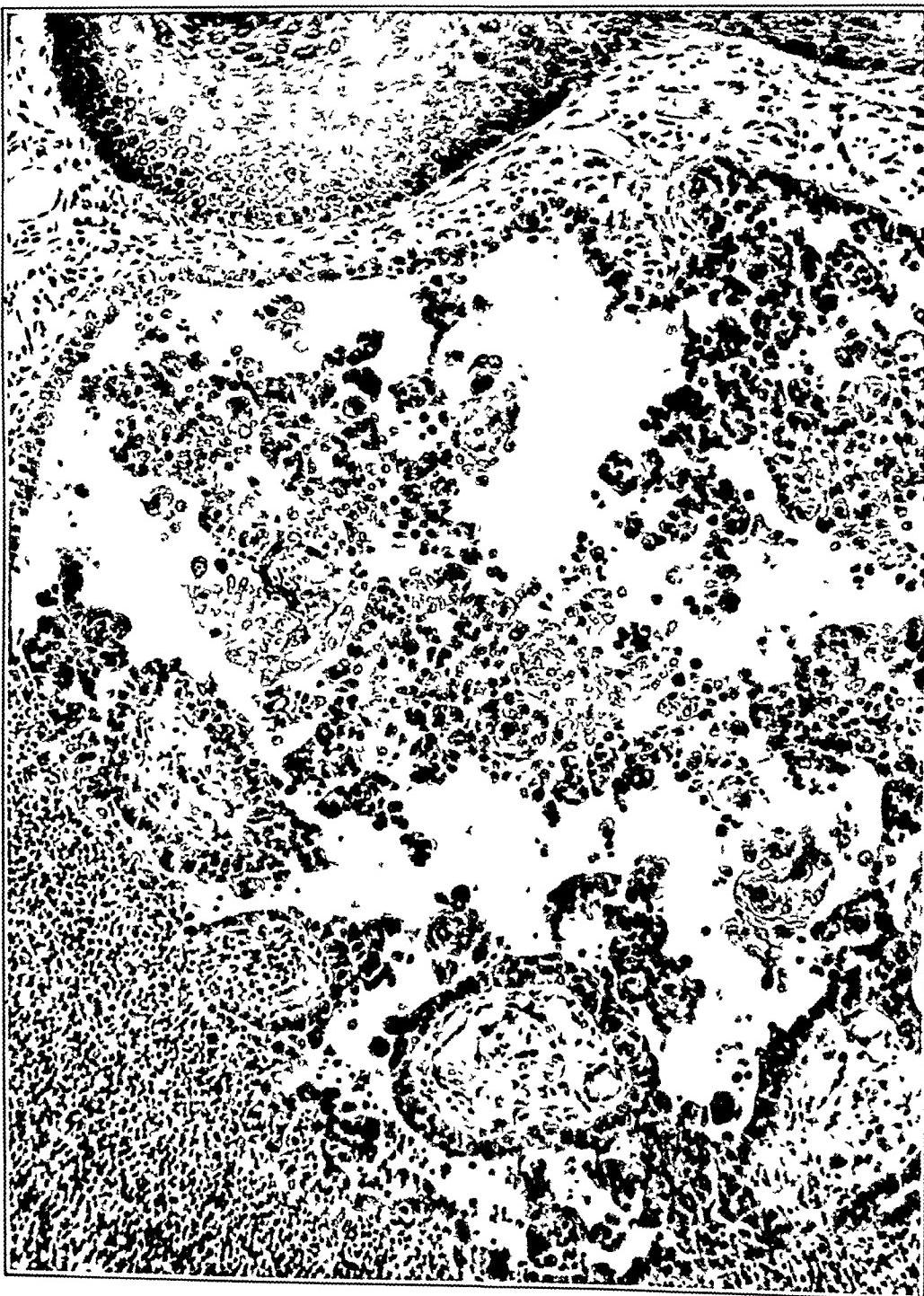


Fig. 6 (case 3).—A large alveolar space lined by glandular epithelium is shown. There are papillary projections into the lumen. The lumen contains desquamated cells, many of which have the appearance of squamous or keratinized cells.

December 1944 a senile keratosis on the right ear was first noticed. It was electrodesiccated but recurred, and others developed nearby. When seen in

small scattered keratohyaline granules. Perinuclear vacuolation was readily apparent. The basal layer of cells and the first few rows of the prickle layer revealed severer changes. A prominent feature, readily observed in figure 5, was the presence of enlarged cells with disintegration of their chromatin content. The chromatin may be dispersed in the form of numerous small granules scattered through a spongy cyto-

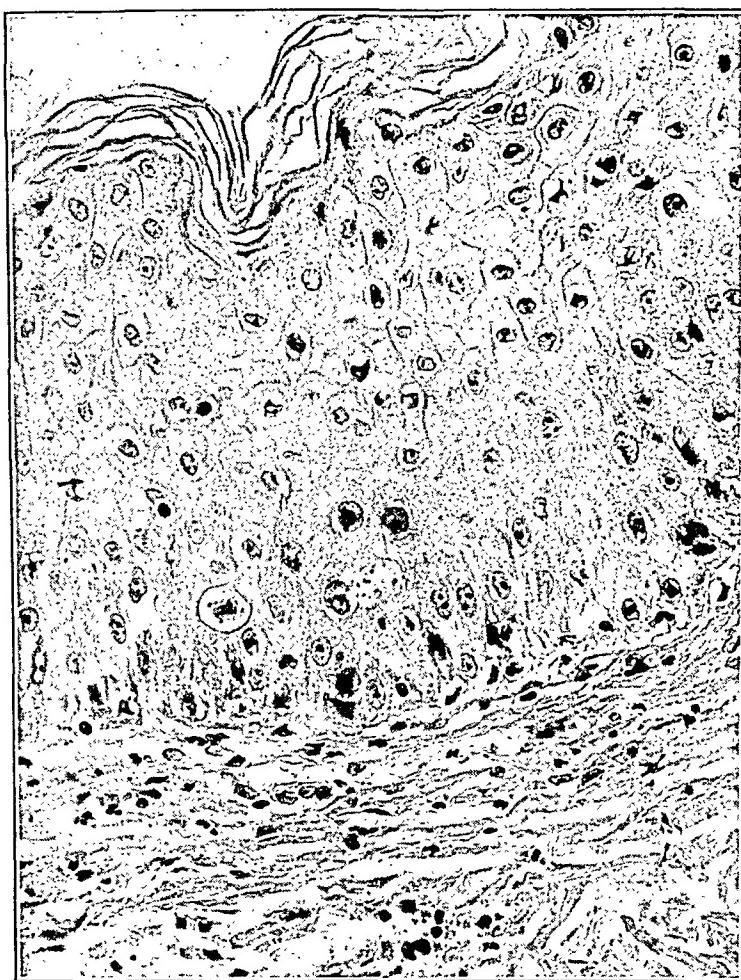


Fig. 5.—Normal skin, twenty-four hours after application of resin of podophyllum in oil. Two "podophyllin cells" are seen.  $\times 200$ .

plasm, suggesting an aborted mitosis, or the nuclear material may be clumped, pyknotic and distorted. Such cells are designated as "podophyllin cells." Other basally placed cells showed degenerative changes, manifested by alteration of nuclear-staining reaction, swelling of the cytoplasm, vacuolation, pyknosis and increase in size and number of nucleoli. The dermis revealed only slight edema and a sparse scattering of lymphocytes. Resin of podophyllum applied beneath the foreskin

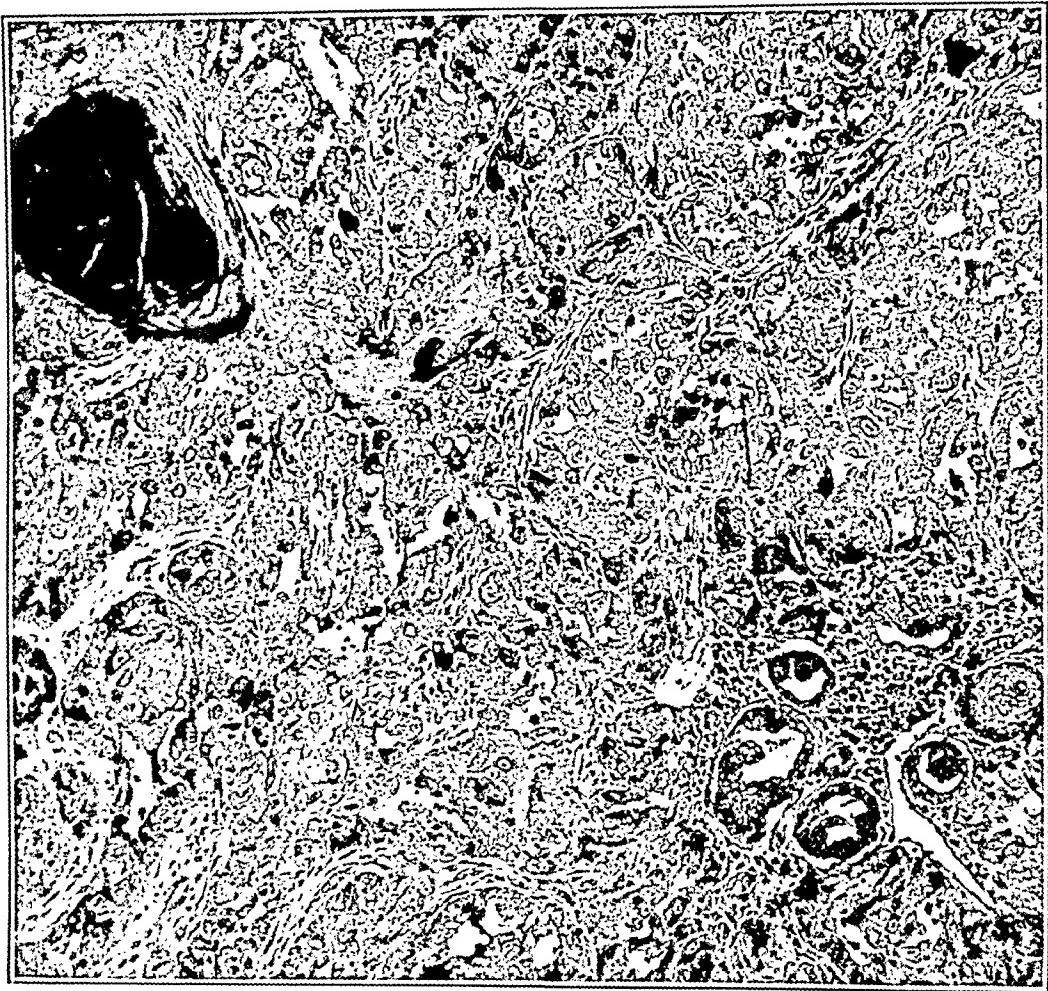


Fig. 8 (case 4).—The tumor is composed of epithelial strands which either are solid or contain a central lumen. Some lumens contain desquamated cornified cells. The centers of some of the solid strands are composed of cornified cells. In the left upper corner, a large area of cornification is seen. In the right lower corner, six sweat ducts are present.

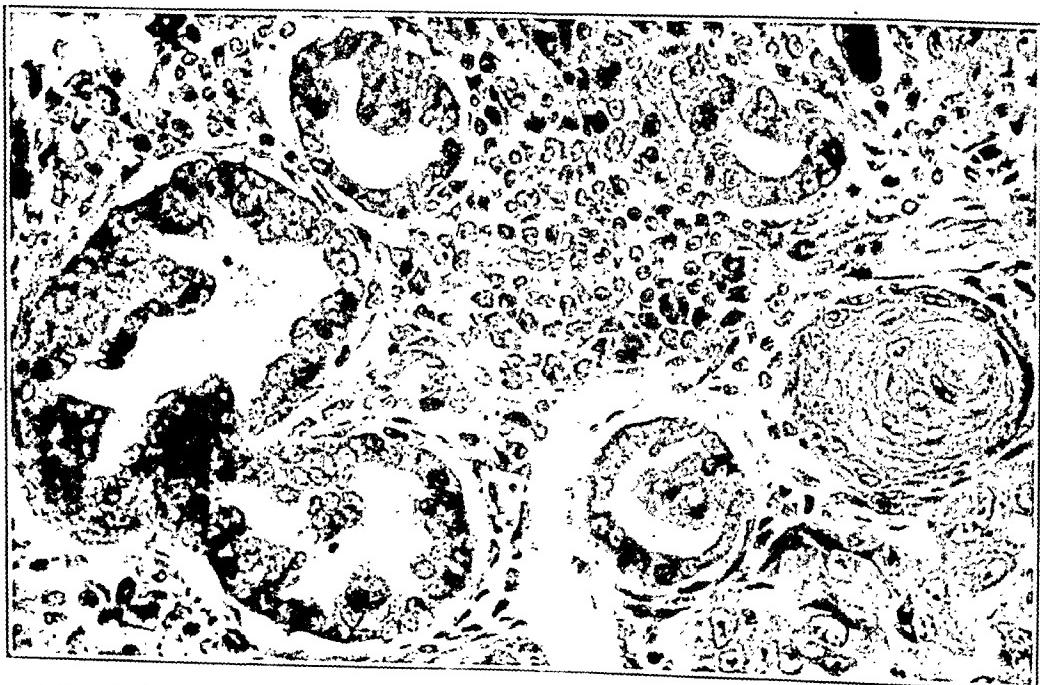


Fig. 9 (case 4).—High magnification of the sweat ducts shown in figure 3. The sweat duct located farthest to the right is of the intraepidermal type (composed of squamous cells), and the others are of the dermal type (composed of glandular cells).

twenty-four hours before circumcision yielded a substantially similar picture.

The loss of intercellular bridges in the upper parts of the prickle layer, together with the accentuation of cell membranes, may be interpreted as a "drying effect." To test this hypothesis the drug was applied to the skin of a patient with extensive eczematous dermatitis. Symmetric plaques of approximately equal severity on each forearm of the patient were chosen. To one, resin of podophyllum was applied and the lesion excised twenty-four hours later. At the same time the contralateral

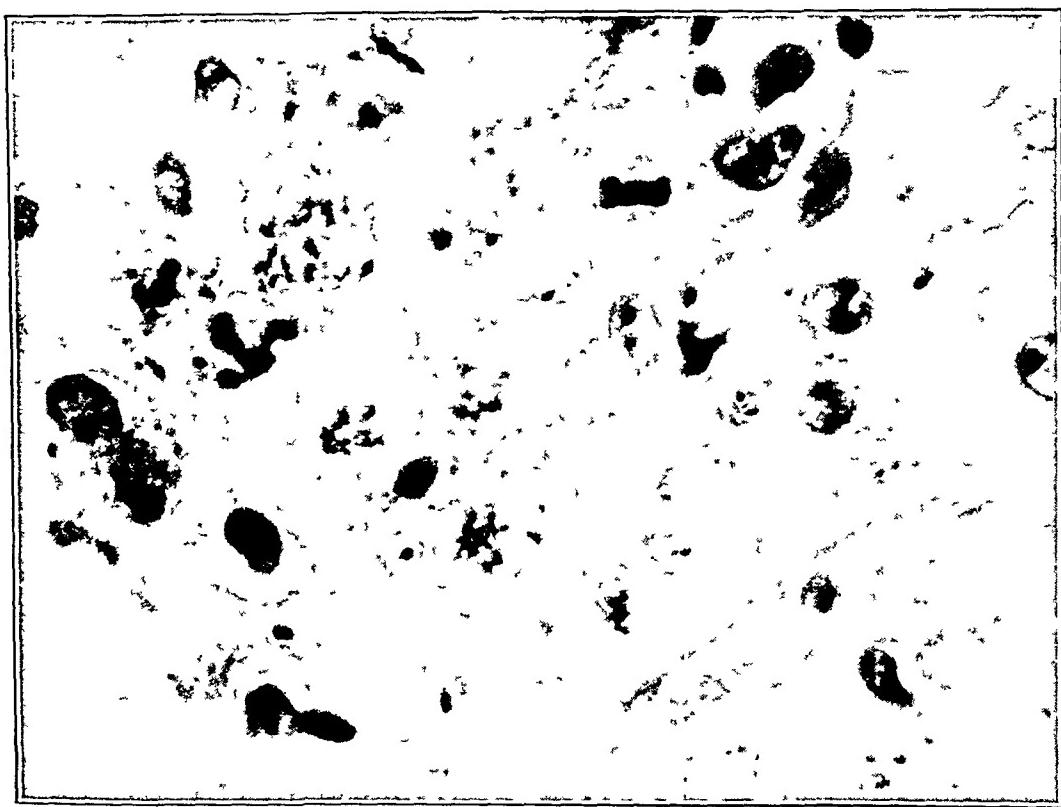


Fig. 6.—"Podophyllin cells" in a plaque of eczematous dermatitis treated with resin of podophyllum. Note the extremely distorted mitotic figures.  $\times 1133$ .

control, untreated, plaque of eczematous dermatitis was similarly examined at biopsy. On microscopic examination the contrast between the two specimens was great. The control section revealed characteristic spongiosis, hydrops and edema, while the area treated with resin of podophyllum exhibited diminution in spongiosis, with changes in the epidermis generally similar to those seen in the upper part of figure 5, that is, loss of intercellular spaces and bridges and intensification of cell membranes. At the same time the deeper portions of the epidermis revealed many "podophyllin cells," with some slight persistence of spongiosis. In figure 6 is seen an oil immersion photomicrograph from the deeper layer of the specimen treated with resin of podophyllum. Several

It was, therefore, concluded that the tumors represented adenocarcinomas of eccrine sweat glands.

The 4 tumors were, however, not pure adenocarcinomas. In areas where the lumens were lined by more than one layer of cells, squamous and keratinized cells frequently formed the inner layers, and many lumens contained desquamated keratinized cells. Furthermore, all 4 tumors contained solid areas composed of squamous and keratinized cells which had the appearance of squamous cell epithelioma, and 3 tumors showed atypical proliferations of their epidermis consistent



Fig. 10.—A normal sweat duct located in normal epidermis is shown. It is surrounded by squamous cells.

with squamous cell epithelioma. The epidermal proliferations merged with the glandular parts of the tumors without clearly defined border.

Thus, the tumors represented adenocarcinomas of sweat glands with areas of squamous cell epithelioma.

It is not admissible to regard the tumors as combinations of two independent types of carcinoma because the two components were so closely interwoven. Although no adequate explanation of the histogenesis of the tumors can be offered, two theories deserve consideration.

cells are shown with complete break-up of chromatin material. These cells were interpreted as in mitosis but with a decided distortion of mitotic activity, dispersion of chromosomes and complete interruption of the usual orderly process. In a preliminary note<sup>14</sup> it has already been observed that these cells are similar to some of the results produced by colchicine and known in the literature as "colchicine figures."<sup>15</sup>

In order to observe the microscopic changes in condylomas treated with resin of podophyllum numerous sections for biopsy were taken from lesions in various stages of regression after treatment. These changes will be described in detail subsequently, but it may be briefly mentioned here that at least two types of action are manifest. The drug produces changes in cells which can be interpreted as distorted mitotic figures of the type shown in figures 5 and 6. This change is apparently specific for a small group of unrelated drugs, including colchicine and resin of podophyllum,<sup>15a</sup> but in addition there is extensive alteration of a degenerative and nonspecific character (fig. 7 A). The "specific" action involving distorted mitosis is not sufficiently widespread in treated condylomas to explain the clinical disappearance of the lesions following treatment. The mechanism of the nonspecific degenerative action is not clear from morphologic studies alone.

Two patients with condylomata acuminata were treated with 30 per cent salicylic acid in liquid petrolatum, and the treated lesions were excised for biopsies twenty-four and forty-eight hours after treatment. Microscopic examination demonstrated a widely different modus operandi for salicylic acid when contrasted with effects of resin of podophyllum. In figure 7 B is a condyloma twenty-four hours after application of salicylic acid in oil. There is a division of the tumor into two zones: The superficial portion reveals general preservation of nuclear structure. The cytoplasm, however, stains a dull brick red. Intercellular bridges may be preserved. There is a sharp line of demarcation between the red-staining surface epithelium and the underlying epithelium, which maintains its normal bluish color. In the figure, a small vesicle is present at the line of demarcation. The proximally situated portion of the tumor shows excellent preservation

14. King, L. S., and Sullivan, M.: The Similarity of Podophyllin and Colchicine Effects and the Use of These Drugs in the Treatment of Condylomata Acuminata, *Science* **104**:244, 1946.

15. (a) Ludford, R. J.: The Action of Toxic Substances upon the Division of Normal and Malignant Cells in Vitro and in Vivo, *Arch. f. exper. Zellforsch.* **18**:411, 1936; (b) Colchicine in the Experimental Chemotherapy of Cancer, *J. Nat. Cancer Inst.* **6**:89, 1945. (c) Lits, F. J.: Recherches sur les réactions cellulaires provoquées par la colchicine, *Arch. internat. de méd. expér.* **11**:811, 1936. (d) Dustin, A. P.: Contribution à l'étude de l'action des poisons caryoclasiques sur les tumeurs animales; action du colchicine sur le sarcome greffe; type Crocker, de la souris, *Bull. Acad. roy. de Belgique* **14**:487, 1934.

of glandular cells, and in areas with several layers of epithelium squamous and partially keratinized cells usually form the inner layers. The lumens are filled with desquamated cells, many of which are partially or completely keratinized. In addition, there are solid areas composed of squamous and keratinized cells which have the appearance of squamous cell epithelioma. The epidermis may show atypical downward proliferation as in squamous cell epithelioma. Atypical eccrine sweat glands and sweat ducts are present within or at the periphery of these tumors.

The presence of glandular and epidermal elements is probably due to the inherent potentiality of the tissue of origin, the sweat ducts, to differentiate into glandular as well as squamous cells (sweat ducts are formed by squamous cells in the epidermis and by glandular cells in the corium). It is possible that metaplasia of glandular into squamous cells also plays a part.

The term adenoacanthoma of sweat glands is suggested as designation for these tumors.

epithelioma in 1928 and stated that there were only 3 cases of metastatic basal cell epithelioma, those of Beadles<sup>sa</sup> and Janeway<sup>sb</sup> and Körbl's case 61.<sup>sc</sup>

A further check of the recent literature has disclosed several possible cases of metastatic basal cell epithelioma. In 1931, Louste, Thibaut, Caillu and Ragu<sup>7</sup> reported a case of basal cell epithelioma of the skin with apparent metastasis to subcutaneous and bony tissue. Their patient first had a lesion on the central part of the forehead, and later a nodule in the pretragal region developed. The histologic diagnosis of the lesion of the forehead was basal cell epithelioma, and the diagnosis of the zygomatic lesion was epidermoid epithelioma, identical with the first lesion. They considered the pretragal lesion a metastasis of the first lesion even though it was not a lymphatic metastasis, and gave the reasons for their conclusions.

Also in 1931, Goodman<sup>8</sup> reported the unusual case of a subcutaneous basal cell epithelioma with nodal metastasis. His patient, S. B., had a nodule under the skin of the right side of the cheek about 2 inches (5 cm.) in front of the ear. The lesion was excised, as were two recurrences. A histologic examination was made of the second recurrence and revealed a basal cell epithelioma. About a year and a half after the second recurrence, the node directly in front of the right ear became enlarged. The node was removed and diagnosed histologically as a basal cell epithelioma (node).

In 1941, De Navasquez<sup>9</sup> reported the case of A. F., who had a basal cell epithelioma on the forehead which was fixed to both the skin and the bone. The lesion was removed, but four years later the patient died of metastases to lungs, spine, ribs, scapulas, pelvis and upper ends of both humeri. Tumor tissue was also observed within a blood vessel of the sternum, indicating that the metastases were blood borne, since there was no evidence of metastasis to the regional lymph node. The metastases all showed the same histologic features of the primary lesion.

Since there are so few cases of metastatic basal cell epithelioma, it was decided to present the only case on record in sixteen years of service at the New York Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital.

6. Montgomery, H.: Basal Squamous Cell Epithelioma, Arch. Dermat. & Syph. **18**:50 (July) 1928.

7. Louste; Thibaut; Caillu, and Ragu: Case of Basal Cell Skin Carcinoma with Apparent Metastasis to Subcutaneous and Bony Tissue, Bull. Soc. franc. de dermat. et syph. **38**:1446, 1931.

8. Goodman, H.: Subcutaneous Basal Cell Epithelioma with Node Metastasis, M. J. & Rec. **134**:271, 1931.

9. De Navasquez, S.: Metastasising Basal Cell Carcinoma, J. Path. & Bact. **53**:437, 1941.

of nuclear and cytoplasmic shape. Occasional normal mitotic figures may be present, but there are no nuclear alterations resembling those of the "podophyllin cells." It is of interest that rare hyaline thrombi may be seen in blood vessels of the dermis following salicylic acid therapy but are not seen following treatment with resin of podophyllum. It is evident that the effect of salicylic acid is that of a simple and direct fixing action on the superficial layers of epithelium, with no evidence of subtle cytologic action. It seems probable that the resin of podophyllum, by contrast, exerts a direct cytotoxic effect, with profound disturbance of the cell metabolism, of a type not yet entirely elucidated.

Two patients with condylomata acuminata were treated with trichloroacetic acid. Histologic alterations essentially similar to those effected by salicylic acid resulted.

The similarity of microscopic changes due to colchicine and resin of podophyllum was noted by one of us (L. S. K.) during the course of this study. Twelve patients with condylomata acuminata were treated with 0.7, 10 and 15 per cent suspensions of colchicine in oil and solutions in alcohol. The clinical cures were more spectacular than those obtained with resin of podophyllum, and the microscopic changes were similar. Comparative studies in skin of rabbits also showed many similarities; the pathologic alterations due to colchicine were more intense and of briefer duration than the changes produced by resin of podophyllum. It should be emphasized that colchicine is not recommended as a routine treatment for condylomata acuminata because of its toxic potentialities. The colchicine-like action of resin of podophyllum, however, should be of interest to investigators in the field of cancer research.

#### SUMMARY AND CONCLUSIONS

1. Resin of podophyllum is a cutaneous sensitizer of the first order.
2. Resin of podophyllum, as used in the treatment of condylomata acuminata, produces irritation of normal mucous membrane if it remains in contact with it for twenty-four or more hours.
3. Fifty patients with condylomata acuminata were treated by topical applications of a 25 per cent suspension of resin of podophyllum in liquid petrolatum according to the technic recommended by Kaplan.<sup>8</sup> One hundred per cent cures were obtained in 48 patients with penile verrucae of the moist type. In 2 patients with chronic perianal verrucae improvement but not complete cure was achieved. The perianal verrucae were of the dry type and approximated verrucae vulgares. One hundred verrucae vulgares were treated with 25 per cent resin of podophyllum in oil and failed to undergo involution.

gram of weight by the simultaneous administration of a total dosage of 1.6 mg. of oxophenarsine hydrochloride by intravenous injection.

As previously reported,<sup>2</sup> the minimal curative dose of penicillin in peanut oil and beeswax was approximately 5,000 units per kilogram when administered intramuscularly once a day for eight days in succession, totaling 40,000 units. As shown in table 4, the intramuscular injection of 1,000 units of penicillin in peanut oil and beeswax once a day for eight days in succession, totaling 8,000 units, was completely curative when oxophenarsine hydrochloride in doses of 0.2 mg. per kilogram was given intravenously at the same time once a day for eight days in succession, totaling 1.6 mg. In the circumstances the simultaneous administration of the oxophenarsine hydrochloride reduced the total minimal curative dose of 40,000 units of penicillin to a total minimal dosage of 8,000 units or less per kilogram.

*Synergistic Activity of Penicillin and Bismuth and Potassium Tartrate.*—As previously stated, the single minimal curative dose of penicillin in peanut oil and beeswax by intramuscular injection was approximately 10,000 units per kilogram.<sup>2</sup> As shown in table 5, the injection of a single dose of 2,000 units in this vehicle was completely curative when administered along with the intramuscular injection of 0.002 Gm. of bismuth and potassium tartrate per kilogram in peanut oil and beeswax. This dose of bismuth and potassium tartrate alone produced temporarily negative results on dark field examinations but was not curative, since the minimal single curative dose of bismuth and potassium tartrate in oil alone is approximately 0.010 Gm. per kilogram in the treatment of acute syphilitic orchitis of rabbits.<sup>3</sup> In the circumstances the simultaneous intramuscular injection of penicillin in peanut oil and beeswax reduced the single curative dose from 10,000 to 2,000 units or less per kilogram when administered simultaneously with one-fifth the minimal single curative dose of bismuth and potassium tartrate in oil.

As previously stated, the minimal curative dose of penicillin in isotonic solution of sodium chloride by intramuscular injection once a day for eight days in succession was approximately 5,000 units per kilogram per dose, totaling 40,000 units. The minimal curative dose of bismuth and potassium tartrate in oil by intermittent intramuscular injection has not been determined, but, as shown in table 6, the intramuscular injection of 1,000 units of penicillin in isotonic solution of sodium chloride per kilogram once a day for eight days in succession, totaling 8,000 units, was completely curative when bismuth and potassium tartrate

3. Kolmer, J. A.; Brown, H., and Rule, A. M.: Studies in the Bismuth Therapy of Syphilis: I. A Comparative Study of the Toxicity and Therapeutic Activity of Bismuth Compounds Commonly Employed in the Treatment of Syphilis, Am. J. Syph., Gonor. & Ven. Dis. 23:7 (Jan.) 1939.

Unfortunately, no single characteristic is sufficient to identify a petroleum product, since many commercial preparations are blends of more than one product. Furthermore, it is common practice to introduce additive agents, inhibitors, soaps, fatty oils and other nonpetroleum materials to petroleum products to impart special properties which are not inherent in petroleum itself. Most present day gasolines contain tetraethyl lead, bromine compounds and dyes. Cutting oils often contain sulfur, chlorine derivatives and/or animal oils. Finally, products of similar characteristics are given different names by different manufacturers, and products sold under a common name by different manufacturers often differ appreciably in their properties.

TABLE 1.—*Physical Properties of Typical Petroleum Products*

	Rubber Solvent	Stoddard Solvent	Kerosene	Mineral Seal Oil	Light Spindle Oil	Light Machine Oil, S. A. E.* 10	Medium Motor Oil, S. A. E.* 20
Specific gravity at 60 F...	0.6506	0.7857	0.8063	0.8333	0.8762	0.8956	0.8927
A. P. I. gravity at 60 F...	68.0	48.5	44.0	38.3	30.0	26.5	27.0
Color, Saybolt.....	+30	+30	+20	+18	2 N. P. A.†	2 N. P. A.†	4 N. P. A.†
Flash point, F.....	-20	105	140	275	335	380	430
Kinematic viscosity, centistokes	0.54 at 77 F.	1.08 at 77 F.	1.55 at 100 F.	4.20 at 100 F.	11.75 at 100 F.	33.2 at 100 F.	123.0 at 100 F.
Pour point, F.....	-75	-60	-40	20	25	25	0
Distillation (A. S. T. M.)					‡	‡	‡
Initial boiling point, F.	140	308	345	506	600	627	713
End point, F.....	226	372	550	607	840	912	...
5% recovered at, F.....	159	314	369	537	625	687	778
10% recovered at, F.....	161	316	378	544	640	704	805
20% recovered at, F.....	165	318	392	551	650	730	835
30% recovered at, F.....	170	320	403	556	665	752	873
40% recovered at, F.....	175	322	416	559	675	768	910
50% recovered at, F.....	180	325	431	563	687	788	940
60% recovered at, F.....	184	328	443	568	700	808	970
70% recovered at, F.....	189	331	464	574	720	820	1,010
80% recovered at, F.....	195	335	481	580	755	845	1,047
90% recovered at, F.....	203	343	504	590	800	865	...
95% recovered at, F.....	209	351	521	605	830	893	...

\* Society of Automotive Engineers.

† N. P. A. indicates National Petroleum Association.

‡ Converted from vacuum distillation at 10 mm.

Therefore, in any approach to a problem involving a petroleum product it is essential that the manufacturer be requested to supply detailed information as to the physical characteristics of the product and the presence of any nonpetroleum constituents. In general, such information can be divulged qualitatively without involving so-called trade secrets, and any reputable petroleum refiner would comply with such a request when the purpose of the inquiry is made known by the physician.

resin of podophyllum in the presence of perspiration has the same dissolving effect on normal epithelial cells as when applied to condylomata acuminata. In checking back in my records, I found I have seen in the last six years 11 patients with contact dermatitis from resin of podophyllum. In each the condition was extremely severe. Dr. Sullivan said that he had not encountered vesication, but in all the patients I saw there were superficial vesication with denudation and considerable edema. Of all the drugs causing contact eruptions encountered in persons who work with pharmaceuticals, resin of podophyllum produces the severest conjunctivitis when the drug is carried to the eye. Four of this group of 11 had associated resin of podophyllum conjunctivitis.

DR. CLINTON W. LANE, St. Louis: Dr. Sullivan is to be thanked for bringing this therapeutic agent to our attention and is to be congratulated on the thoroughness and conservatism of his paper. Time did not permit him to enumerate all the dangers which occur in the employment of this drug.

In the use of podophyllum locally two precautions should always be observed. It is definitely a job for the physician and not one for the patient, and it should never be applied to any verruca in close proximity to the eye.

An experience in proof of point 1 occurred when a young prospective bridegroom consulted me for premarital removal of a number of verrucae acuminata in the perianal and perineal regions. The successful use of resin of podophyllum in the armed forces had been reported to me, and the patient was given a 25 per cent suspension in oil to apply carefully to the warts. On the following night I was summoned to the home to find the patient in excruciating pain and most apprehensive because of a pronounced erythema and a tremendous edema of the penis, scrotum, perineum and perianal region. A ten day period with the area under cool compresses and soothing local applications was necessary before the inflammation subsided.

Podophyllum has also been reported as a successful agent in the removal of warts other than the venereal type. If such warts are on the face, and particularly if close to the eye, extreme caution must be used in application of the drug. A pharmacist whose verrucae acuminata on the prepuce had been successfully removed with one application of the drug inquired and was informed of the ingredients of the suspension. He compounded a similar prescription and applied it to a small wart on the margin of an upper eyelid. A severe inflammation of the cornea, sclera and conjunctiva occurred, and three weeks of treatment from an ophthalmologist was necessary to prevent serious and permanent damage to the eye.

DR. C. L. McCARTHY, Washington, D. C.: I believe that the successful use of this drug brings up one question. Formerly I was convinced that condylomata acuminatum was exactly the same lesion as a wart but that it occurred in a hot, moist place; however, it does not touch the ordinary wart, in my experience, even though it is a new, soft wart. The question arises now, is condylomata acuminatum the same thing as an ordinary wart?

DR. E. WILLIAM ABRAMOWITZ, New York: I want to congratulate the authors on their excellent presentation.

There is no doubt about the effective action of resin of podophyllum (podophyllin) in venereal warts. The drug is now listed in the National Formulary as a drastic purgative, and it has caused irritation of the anal region. I always considered it a cutaneous irritant.

Its action is apparently contrary to the treatment of other types of verrucae. The warts become more hyperkeratotic even though concurrent therapy (roentgen ray, vaccine and other treatment) is being employed.

results in patch tests, representing, perhaps, a "twilight zone" of irritability. It is on these materials that clinical study was performed.

*Persons Tested.*—Patch tests were performed on the following groups:<sup>2</sup> Group I included normal (healthy) persons, both white and

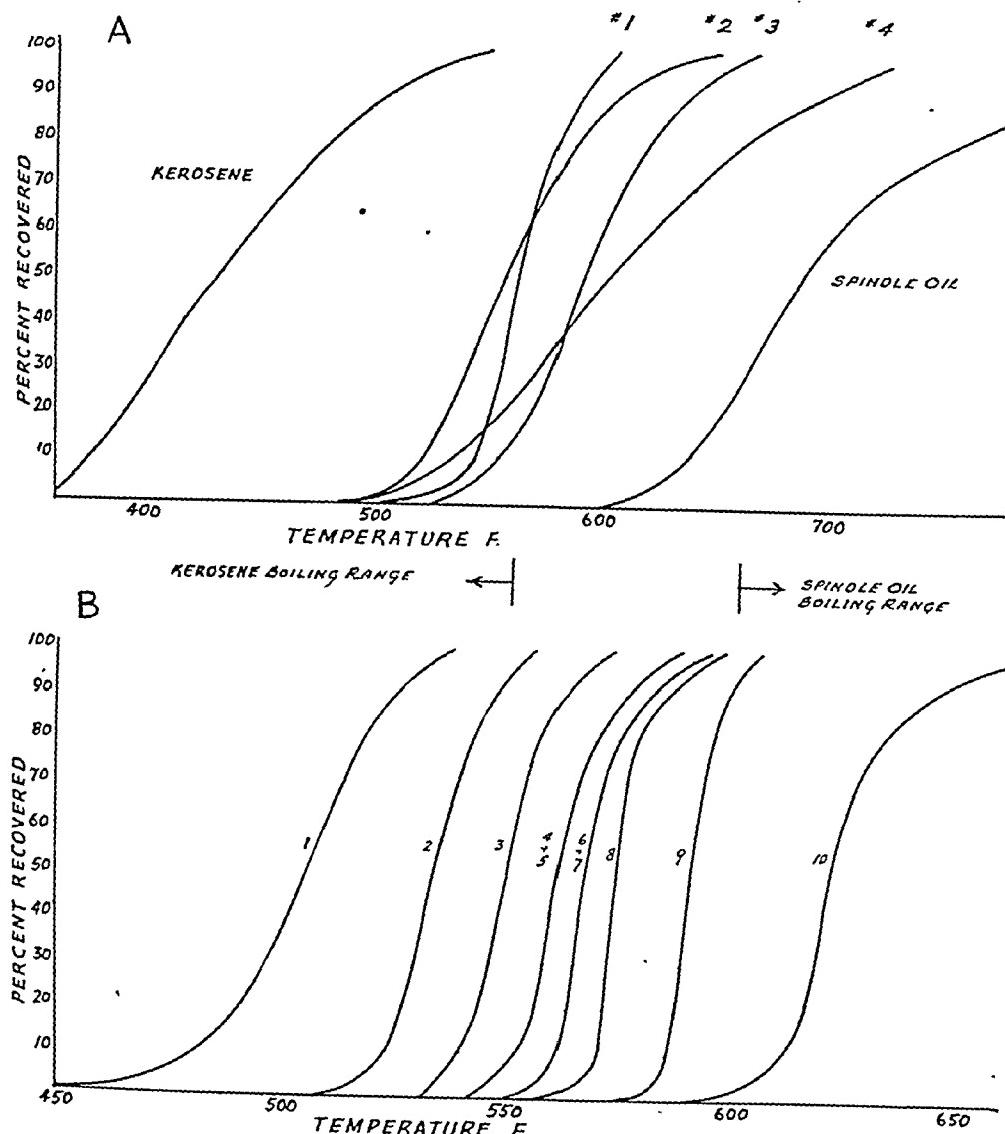


Chart 2.—A, boiling ranges of mineral seal oils. B, boiling ranges of 10 per cent fractions of mineral seal oil no. 1.

Negro, not regularly exposed to petroleum products. Group II included industrial workers whose dermatitis was attributed to petroleum solvents used in their work. Group III consisted of patients with diffuse

2. In performing patch tests, a piece of four ply gauze 1 inch (2.5 cm.) square was used. In each test 6 drops of the solvent or oil was applied to the gauze, covered with wax paper and maintained at the site for twenty-four hours. Positive reactions were graded as follows: mild erythema 1 plus, well defined erythema 2 plus, erythema with edema and with or without a few vesicles 3 plus and erythema, edema and many vesicles or serous exudation 4 plus.

action of a naphthenic fraction of the same boiling range, a sample was specially prepared from a naphthenic crude petroleum and refined in the conventional manner employed for paraffinic distillates of kerosene. Tests were performed with this naphthenic kerosene on 10 normal (healthy) white persons. All reacted positively, and 7 had 4 plus reactions. Of persons tested (white as well as Negro) with both types of kerosene, the reaction to the naphthenic fraction was greater.

This study evidences a varying tolerance of the skin of white persons to paraffinic kerosene, a greater tolerance of the skin of Negroes and a greater irritant action of naphthenic kerosene compared with that of

TABLE 3.—*Ten Per Cent Fractions from Mineral Seal Oil No. 1*

	No. 1 0-10 %	No. 2 11-20 %	No. 3 21-30 %	No. 4 31-40 %	No. 5 41-50 %	No. 6 51-60 %	No. 7 61-70 %	No. 8 71-80 %	No. 9 81-90 %	No. 10 91-100 %
Specific gravity at 60 F.....	0.8309	0.8324	0.8314	0.8324	0.8324	0.8328	0.8328	0.8328	0.8353	0.8463
A. P. I. gravity at 60 F.....	38.8	38.5	38.7	38.5	38.5	38.4	38.4	38.4	37.8	35.7
Kinematic viscosity, centistokes at 100 F.....	2.75	3.43	3.93	4.28	4.39	4.57	4.54	4.74	5.47	7.50
Distillation (A. S. T. M.)										
Initial boiling point, F.....	436	510	532	540	544	548	553	559	575	583
End point, F.....	534	553	570	584	586	594	583	585	603	663
5% recovered at, F.....	474	520	536	547	550	558	560	568	584	611
10% recovered at, F.....	483	524	540	556	553	560	562	570	585	614
20% recovered at, F.....	492	527	544	558	555	562	564	571	587	616
30% recovered at, F.....	498	530	546	559	557	564	565	572	588	618
40% recovered at, F.....	502	532	548	560	559	566	566	573	589	620
50% recovered at, F.....	506	534	550	562	561	568	567	574	590	621
60% recovered at, F.....	510	536	552	564	563	570	569	575	592	623
70% recovered at, F.....	514	539	554	566	565	573	570	576	593	626
80% recovered at, F.....	519	542	557	568	569	576	572	577	595	631
90% recovered at, F.....	525	547	562	574	576	584	577	580	598	643
95% recovered at, F.....	530	550	566	578	581	590	580	583	600	662

paraffinic. The latter observation is consistent with the observation of Jordan<sup>3</sup> that the irritant action of petroleum compounds is increased by the presence of naphthenes (polymethylene compounds).

*Patch Tests with Mineral Seal Oil and Light Spindle Oil.*—In a communication<sup>1a</sup> by one of us (J. V. K.) report was made of dermatitis from mineral seal oil. It was stated: "In these patients the dermatitis was clinically of the sensitization type, appearing on the hands and forearms and in some on the face, usually months after initial exposure." Patch tests with mineral seal oil gave positive reactions on these patients and negative results on 8 persons used as controls. For this reason it was concluded that mineral seal oil was not a primary irritant.<sup>4</sup> Sub-

3. Jordan, O.: The Technicology of Solvents, New York, Chemical Publishing Company, 1937.

(Footnotes continued on next page)

## ACROKERATOSIS VERRUCIFORMIS (HOPF)

Report of Fourteen Cases in One Family in Four Generations,  
with a Review of the Literature

MEYER L. NIEDELMAN, M.D.

PHILADELPHIA

**I**N A RECENT study of a wartlike eruption of the hands and feet in a boy of 17 years, investigation revealed a familial incidence of the disease involving no less than 14 members of the family in four generations. Careful histologic examination of the lesions seemed to warrant a diagnosis of Hopf's acrokeratosis verruciformis.

### REPORT OF CASES

*History.*—P. D., a 17 year old boy of Italian parentage, consulted me for warts on his hands (fig. 1), which, according to the boy's mother, had made their appearance when he was 9 months of age. He also presented acne vulgaris of the face. The mother and his 2 sisters suffered from similar lesions (figs. 2 and 3), and still further investigation led to the discovery of no less than 14 members of this family afflicted in the same manner over four generations. The genetic history is shown in figure 4. In all these patients, the lesions had first appeared when the patients were between the ages of 6 months and 1 year. Consanguinity could not be demonstrated. Past and present histories were noncontributory. No other lesions could be discovered.

*Physical Examination.*—No abnormalities were found except an ichthyotic skin. All the patients were rather dark skinned.

*Dermatologic Examination.*—All the patients in this family that were examined had lesions on the dorsal and palmar surfaces of the hands and dorsa of the feet except R. D., aged 10 years, who had lesions only on her hands. Many had lesions extending above the wrist and ankles. The verruca-plana-like papules were discrete, but many were confluent. The papules varied from the size of a pinpoint to 4 mm. in diameter, and some were elevated 1 to 2 mm. Those on the palms and soles were few, disappearing toward the center. There were no subjective symptoms. All had mild keratosis of the palms and soles. The color of the lesions varied from a pinkish flesh color to light brown. The lesions on the dorsa were flat and smooth, only a few appearing verrucous. Many were polygonal and resembled lichen planus. Even where the papules had become confluent, their individual configuration was not lost. The resistance to section when a biopsy was performed resembled that felt on cutting fibrous tissue. Many of the lesions had a sheen. In some cases they extended as far as 3 inches (7.6 cm.) above the wrist and 2 inches (5 cm.) above the ankle. On the palms and soles, the lesions appeared embedded and were shotty to the feel. They were discrete and could better be felt than seen. On stretching the skin, the papules rose above the surface, possibly owing to pressure.

and 10. The percentage of positive reactions to the eczematogenous noxae was not essentially different than that of patients in group II.

Since patients with eczematous dermatitis (group III) reacted to the ten fractions in a manner comparable to patients with dermatitis caused by solvents (group II), it appears that the dermatitis of such patients (group II) is not the expression of a hypersensitivity solely to such solvents. Petroleum solvents apparently are eczematogenous noxae, comparable to other noxae, prolonged exposure to which lowers the threshold of irritability of the skin, predisposing to a nonspecific irritability of the skin (eczematous dermatitis).<sup>12</sup>

• *Practical Applications of These Studies.*—The foremen of some of the workers who had dermatitis from exposure to petroleum solvents have frequently remarked that other workers doing the same work have never had dermatitis. It is to be noted, however, that the period of exposure to solvents in the group of 45 workers with dermatitis extended up to thirty years. The observation that the general run of industrial workers are apparently immune to petroleum solvents is consistent with the varying reaction to patch tests of normal persons comprising group I. Of practical importance is the question: Will dermatitis eventually develop in all workers exposed to solvents?<sup>13</sup>

To reduce the hazard of dermatitis from petroleum solvents, it is desirable, provided gloves or other mechanical protection cannot be employed, to use a solvent with as high a boiling range as is consistent with the purpose for which it is to be used. Mineral seal oil (of the same boiling range as sample 1) should be given preference to kerosene; spindle oil of high viscosity should be preferred to one of low viscosity. For some industrial uses (for example, the cleaning of printing presses) rapid solvent action is an important requisite. Therefore solvents of high boiling range may not be appropriate. This, however, may not apply to other work entailing exposure of the hands to solvents (for example, the cleaning of mechanical parts). Kerosene of paraffinic origin should be preferred to one of naphthenic origin. In previous studies<sup>1</sup> it was stated that "A conspicuous mechanism of the acquisition of dermatitis was the use of solvents . . . to clean mechanical parts,

12. The employment of the ten fractions for patch testing affords a standardized qualitative manner of determining tolerance of the skin to external irritants. For this reason they are preferable to the commonly employed eczematogenous noxae.

13. This is concerned with predisposing causes of occupational dermatoses and is in relation to circumstances that alter the physiology and defensive mechanism of the skin. There is evidence that an increase in degree of exposure to a noxae or injury to the skin, such as a burn, predisposes to dermatitis. The defensive mechanism of the skin is doubtless dependent on an interplay of a number of physiologic functions, which, in turn, are altered by a variety of factors such as diet, fatigue and hygiene of the skin.

*Laboratory Examination.*—Serologic tests for syphilis gave negative results. The blood cell count and urine were normal. The basal metabolic rate of M.D. was minus 15 per cent. The blood cholesterol level was normal.

*Histologic Examination* (performed by Dr. Fred D. Weidman).—A biopsy specimen taken from the dorsum of the hand of the patient P. D. was examined.

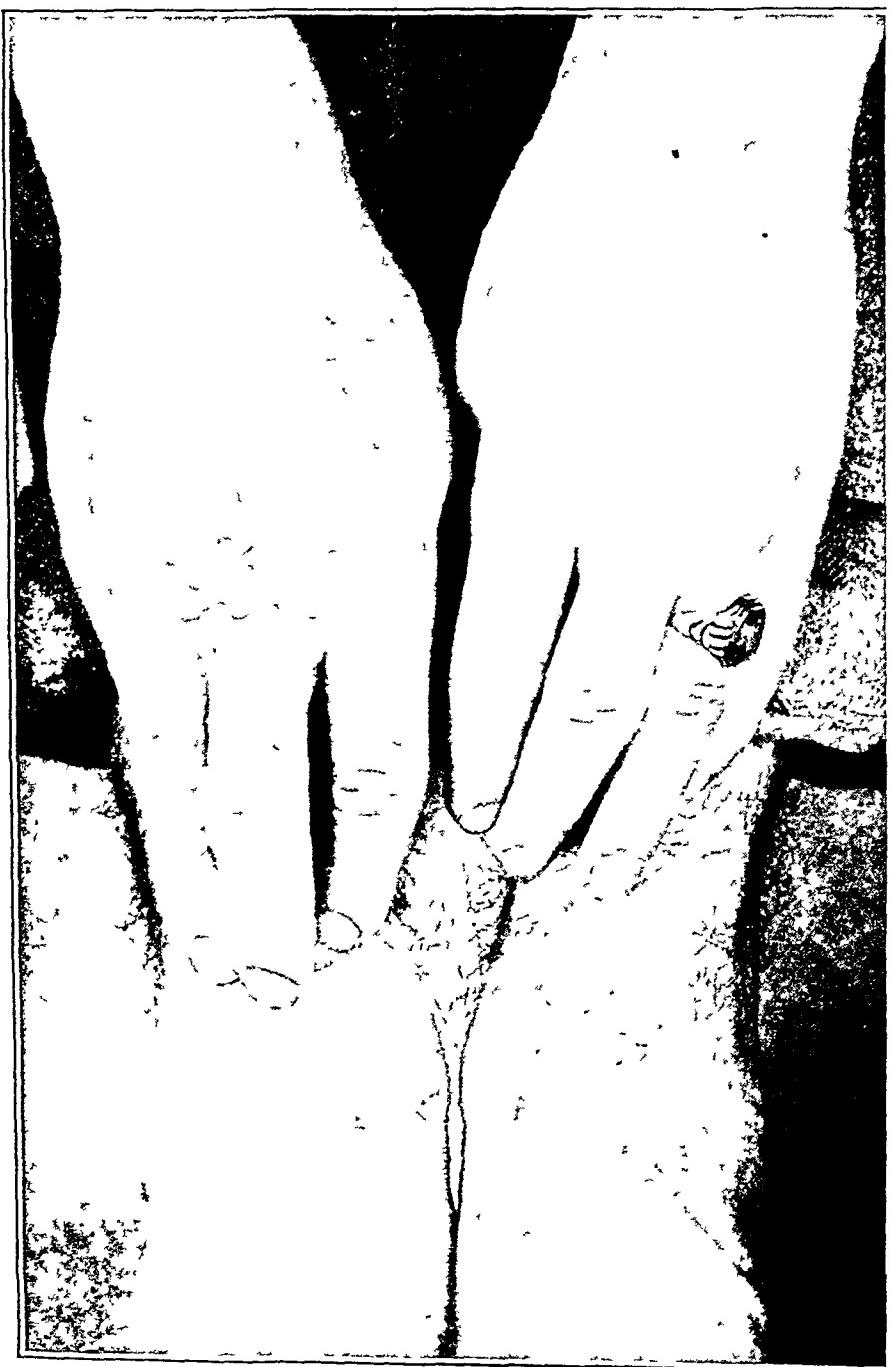


Fig. 1.—P. D. Verruca-plana-like lesions on dorsum of hands and feet. There is some confluence of the lesions on the inner aspects of the hands.

Microscopically it revealed (fig. 5) one of the purest examples of acanthosis and hyperkeratosis that could be imagined. On the surface of the skin, the stratum corneum showed pure hyperkeratosis without a trace of parakeratosis. It was

to which he was exposed. Further questioning elicited the likely cause of the dermatitis. For years he used Oakite for cleansing. The powder was applied freely on the palms and then rubbed over the hands and forearms. After recovery, we counseled his return to the same work with cessation of this method of cleansing.

Patch tests with the aforementioned ten fractions were of value in differentiating dermatitis due to petroleum solvents from that arising as an allergic reaction to oil, as illustrated in the following case:

A young woman was employed for two years inspecting ball bearings. With ungloved hands she immersed the bearings in a pan containing light spindle oil and then in a pan containing kerosene. Dermatitis first appeared on her arms, which she attributed to contact with her soiled hands when she stood with arms folded across her chest. Subsequently the hands, forearms, face, neck and V of the chest became affected. Involvement of the face and neck suggested an allergic reaction. This was supported by patch tests. The ten fractions reacted as follows:

Numbers										
1	2	3	4	5	6	7	8	9	10	
2+	1+	1+	1+	—	—	—	—	—	—	3+

Negative results were obtained with the four samples of mineral seal oil. The slight reactions to the ten fractions were inconsistent with dermatitis arising from kerosene. On the contrary, they evidenced a good degree of tolerance. The 3 plus reaction to fraction 10 suggested an allergic reaction to spindle oil. The dermatitis promptly disappeared after cessation of work. On the basis of these patch tests we counseled her return to work entailing exposure to petroleum solvents but not to spindle oil.

#### SUMMARY

1. Report is made of results of patch tests with petroleum solvents and oils essentially of paraffinic origin ranging from kerosene (initial boiling point 345 F.) to light spindle oil (end boiling point 840 F.) performed on normal white persons, Negroes, industrial workers with eczematous dermatitis caused by petroleum solvents and patients with eczematous dermatitis not caused by solvents.
2. There is a correlation between the boiling ranges of petroleum products of paraffinic origin and their irritant action. Irritant action like defatting action decreases as the boiling range increases.
3. Petroleum solvents with boiling ranges up to and including kerosene are primary irritants. This may or may not be due entirely to their defatting action.
4. The cutaneous reaction to petroleum oils with boiling ranges intermediate between kerosene and the viscous lubricants varied considerably in normal persons, from no reaction to varying degrees of positive reactions. The skin of the Negroes showed a high degree of tolerance. There was a lessened degree of tolerance of the skin of workers with dermatitis caused by solvents and of patients with dermatitis not caused by solvents.

excessively thick, being three or four times the thickness of the rest of the epidermis. Correspondingly, the stratum granulosum was thick and conspicuous, with moderately hyperplastic prickle cells. The general configuration of the inter-papillary pegs was well preserved. At most, these were only broadened or thinned,



Fig. 2.—Mother of P. D., with similar lesions on the dorsa of the hands and feet.

and all of them extended downward to a uniform level. No pathologic changes could be demonstrated in the corium.

The histologic picture was exactly that of acrokeratosis verruciformis. Epidermodysplasia verruciformis could be reasonably excluded, especially if it be assumed that all patients with the latter disease show vacuolation in the epidermis. Incidentally, I am of the opinion that vacuolation might represent only an occasional and secondary complication of the keratinizing processes of epidermodysplasia verruciformis and that the knowledge of these conditions at present is

Allergy is highly specific. In the case of solvent dermatitis, any of the classes of solvents would cause similar dermatitis in the case of patients with dry skins.

As the authors bring out one must not lose sight of the fact that, under actual occupational conditions, these petroleum distillates are often treated with sulfur and chlorine compounds when made into actual cutting oils and that to these sulfurized, chlorinated bases other chemicals—called additives—are added in order to give certain desirable properties to the cutting oils. Some of these additives, such as the chlorinated hydrocarbons (carbon tetrachloride, chloronaphthalenes and chlorodiphenyls) and the phenolics (inhibitors) are themselves primary irritants and sensitizers. Moreover, the heat generated at the point of the cutting tool often forms decomposition products, such as  $\text{SO}_2$  and  $\text{H}_2\text{S}$ , which are irritants; finally, the alloy of which the cutting edge is made contains sensitizing metals, such as cobalt, and as the edge of the tool wears away the oil will contain them.

The fat solvent properties of the petroleum distillates are only one of the factors by which they as a class cause dermatitis. It is true that this is the principal cause of dermatitis from the low boiling fraction, but they also have keratogenic and sensitizing properties. The type of dermatitis caused by the low boiling fractions is usually of the eczematoid type, either acute or chronic, on the hands and forearms. The acute type occurs chiefly on the fingers, interdigital spaces and dorsa of the hands, and the chronic type occurs on the palms as well. Petroleum distillates with high boiling points have less defatting action but more keratogenic action. They cause comedos, acnes, photosensitivity, melanosis, keratoses and epitheliomas. The oils from various portions of the globe differ in these keratogenic properties; for instance, the oils derived from Scotch shale have greater carcinogenic properties than our American oils, hence the higher incidence of "mule-spinners' cancer" in England. Twort stated that the degree of fluorescence of an oil is an index of its carcinogenic properties. Benzopyrene is said to be the principal carcinogen in petroleum oils.

The heat of the fractional distillation and of the cracking process forms certain irritant chemicals which were not in the original crude oil, and these chemicals remain mostly in the final heavy oils and the residual tars, asphalt and pitch. While epithelioma, melanosis and photosensitivity will develop in only a small proportion of workers, our experience in industry shows that dermatitis, folliculitis, comedos and acne from petroleum distillates will develop in any one if there is sufficient exposure and lack of proper protectives and lack of scrupulous cleanliness.

I do not advocate preemployment patch tests for new workers who are to work with petroleum solvents. Patch tests can only pick out the workers whose skins are already predisposed to dermatitis. Patch tests are not necessary to do this. Such dry or senile skins can be seen at a glance by an experienced physician. Moreover, if a person with a dry or senile skin uses proper protective clothing, proper emollient protective creams and scrupulous cleanliness he can avoid dermatitis. In workers having oily, thick skins, who may not react to the patch test, dermatitis will in time develop if they do not take the proper preventive precautions because as they get older their skin becomes dryer. Continued exposure to the solvents, exhausts and injures the glands in the skin. Comedos and acnes are more likely to form on oily skin which passed the preemployment patch test, from continued exposure; finally, epithelioma is more likely to develop in older workers regardless of the results of preemployment patch tests. An observant dermatologist can tell by inspection the type of skin which can best withstand

not sufficient to permit a convincing differentiation. From what is known at present, a diagnosis of acrokeratosis would seem most appropriate.

With regard to associated symptoms mentioned in isolated instances by other writers, it is emphasized that rubbing the lesions did not produce vesicles, the blood cholesterol level was normal, and the cornea

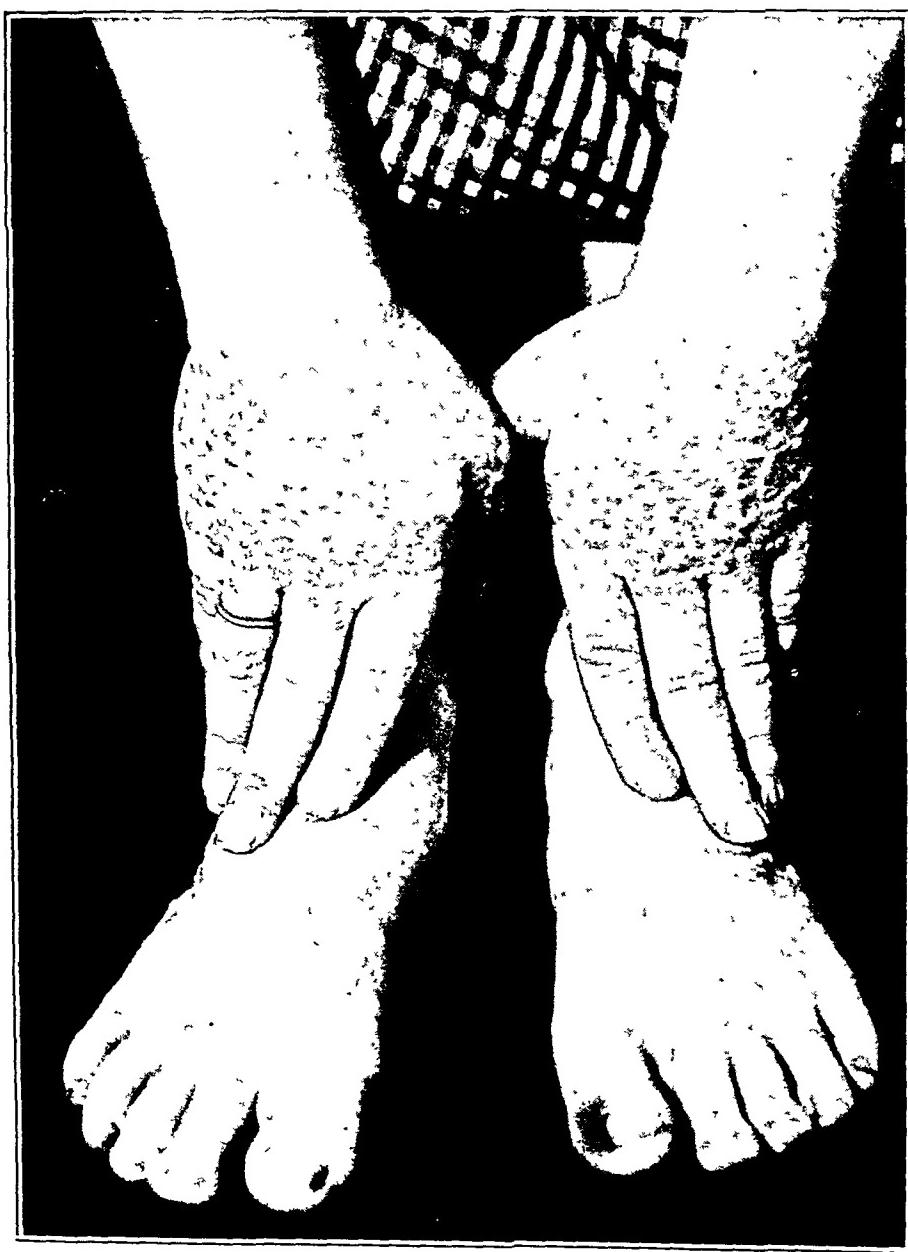


Fig. 3.—Sister of P. D. The lesions are numerous and typical of acrokeratosis verruciformis.

examined in several cases was normal, as likewise the mucosae. There was no family history of epilepsy, although the patients were not highly intelligent. The nails were rather brittle, and the patients did not perspire freely. The skin, as mentioned, was thick and dark.

tested was oil, no evaporation occurred. It is to be doubted whether the 1 plus reactions have any practical significance.

The degree of positive reactions correlated the range of the fractions. Two and 3 plus reactions predominated, with some 4 plus reactions in the tests with fractions 1 to 5, whereas 2 plus and 1 plus reactions predominated in the tests with 6 to 10.

Briefly, our study showed that the irritant action correlated the boiling range; as the boiling range increased, the irritant action decreased. The defatting action is also in inverse ratio with the boiling range. It is to be emphasized that the correlation of irritant action with the boiling range applied to petroleum products of paraffinic origin. Irritant action of kerosene of naphthenic origin and of a solvent of high aromatic content obtained from a cracking process employed in obtaining high octane gasoline was much greater than that of solvents of paraffinic origin with the same boiling range. We believe that this is not generally known.

An interesting question suggested by our studies is this: Can a solvent be produced that exerts a minimum defatting action on the sebum in the direction of minimizing irritant action on the skin?

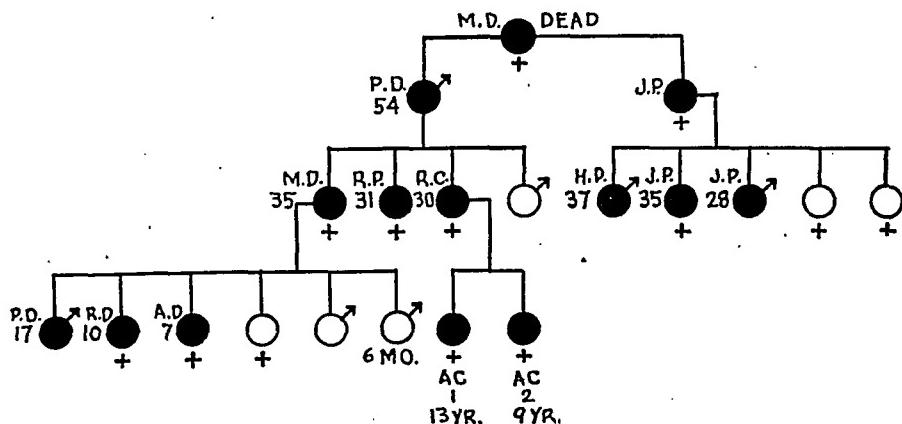


Fig. 4.—Genetic history of patients (filled-in symbols) with acrokeratosis verruciformis. There were 4 affected males, 10 affected females, 3 unaffected males and 3 unaffected females.

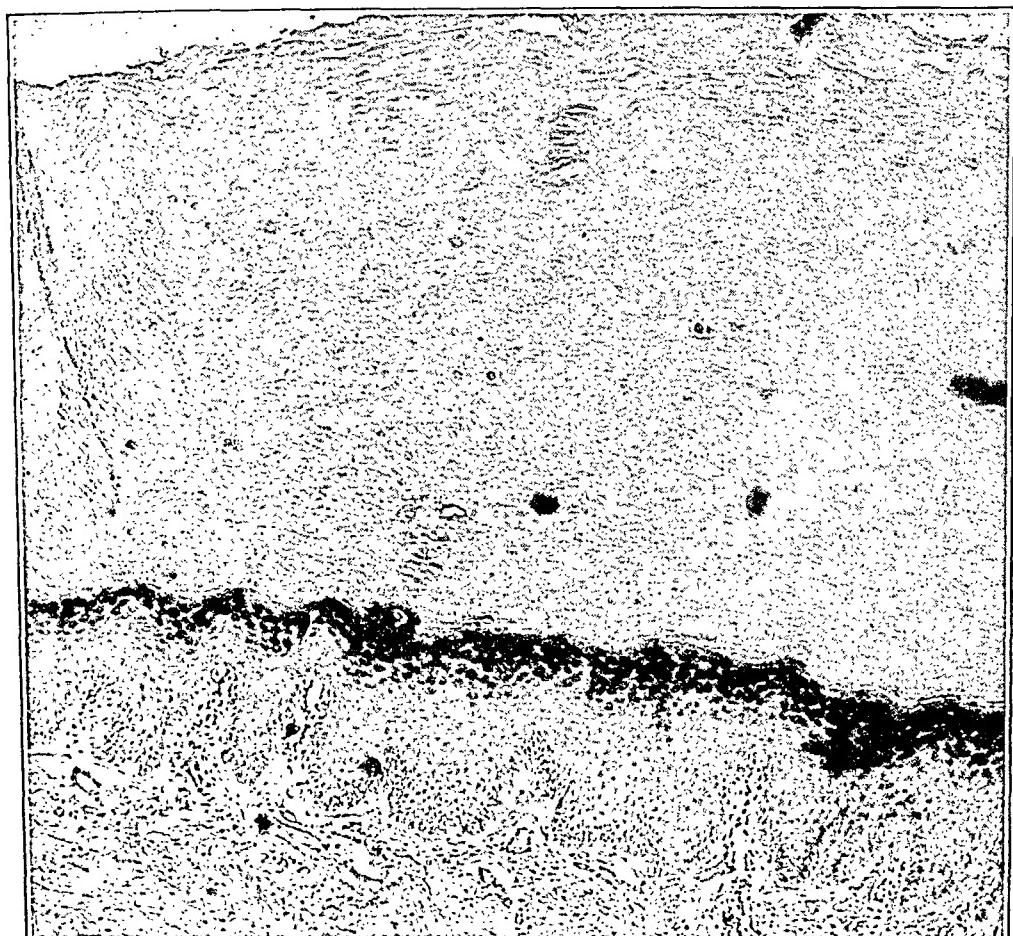


Fig. 5.—Photomicrograph of section from the dorsum of the hand of P. D., showing hyperkeratosis and acanthosis. No vacuolation in the epidermis is seen.

sensitization and the chemical configuration of these substances. In the case of the nitrochlorobenzenes, Landsteiner and Jacobs<sup>1</sup> have shown a reasonable and definite correlation between the sensitizing ability of a particular nitrochlorobenzene and the reactivity of a chlorine atom or a nitro group. They stated as follows:

In most cases a correspondence was evinced between lability of Cl and NO<sub>2</sub>, when treated with alkali, and sensitizing effects; and in all cases tested there was agreement between ability to sensitize and formation of substitution compounds with an organic base. It seems reasonable to assume that in the animal a reaction takes place by which substances are converted into antigens. How and with what substances, proteins or others, a combination of the active compounds occurs, remains to be ascertained.

In the case of other compounds which are good sensitizers, such as paranitrosodimethylaniline and paraphenylenediamine, different types of reactions with the bodily constituents are to be expected, but it seems not unreasonable to believe that a correlation exists between the ability of the compound to sensitize and its ability, or the ability of its breakdown products, to enter into combination with some of the body substances. This question is discussed in somewhat greater detail in a recent article by Gell and his colleagues.<sup>2</sup> The reason that persons acquire eczematous sensitizations to a much wider variety of substances than can be used to produce these sensitizations experimentally is not known. The explanation probably lies in the persons rather than in the chemicals. There may be some peculiar genetic predisposition to sensitizations in general or to the allergen in question in particular (Landsteiner, Rostenberg and Sulzberger<sup>3</sup>), or there may have been some special favoring circumstance at the time the allergen was encountered, such as a local inflammation.

#### SITE TO WHICH THE ALLERGEN MUST BE APPLIED

Ordinarily in the development of spontaneous eczematous sensitization the allergen comes into contact with only the epidermis or possibly the external mucous membranes, and in view of the fact that eczematous sensitizations do not seem to arise from the vast majority of substances which are taken internally the question naturally arises whether the allergen must come into contact with the epidermis in order for eczematous sensitization to be engendered. In spontane-

1. Landsteiner, K., and Jacobs, J.: Studies on the Sensitization of Animals with Simple Chemical Compounds: II., *J. Exper. Med.* **64**:625, 1936.

2. Gell, P. G. H.; Harington, C. R., and Rivers, R. P.: The Antigenic Function of Simple Chemical Compounds: Production of Precipitins in Rabbits, *Brit. J. Exper. Path.* **27**:19, 1946.

3. Landsteiner, K.; Rostenberg, A., Jr., and Sulzberger, M. B.: Individual Differences in Susceptibility to Eczematous Sensitization with Simple Chemical Substances, *J. Invest. Dermat.* **2**:25, 1939.

## COMMENT AND REVIEW

In February 1930, at a meeting of the Hamburg-Altona Dermatological Society, Gustav Hopf<sup>1</sup> presented a case of unusual, partially verruciform keratosis, which did not fit into hitherto described entities. Six months later, he encountered another case of the same kind of circumscribed, disseminated keratosis of the dorsa of the hands and feet. The dorsa of both hands were thickly and symmetrically covered with a mosaic of flat elevations, giving the impression of shagreened leather and leaving only scant normal skin. At first glance, the dorsum of the hand appeared rough and tessellated like a grater. At the age of puberty, symmetric red, verrucous areas the size of a dollar had appeared in the center of the dorsum of each hand. These foci enlarged rapidly, and after fourteen days the dorsa of both hands were completely covered; they remained unchanged thereafter. At the time of examination Hopf's patient was 31 years old. The nails were brittle and chipped easily. Attempts to remove the wartlike lesions with caustics had failed. The eruption extended to the basal phalanges of the fingers, about 2 fingerbreadths up the forearm and in scattered foci to the terminal phalanges. A wavy margin was formed against the volar surface. Only on the ulnar aspect did the efflorescences extend to the thenar eminences.

The individual foci were round, polygonal or oval efflorescences varying in size from that of hemp seeds to that of lentils, sharply defined and occasionally confluescing papular keratotic lesions. These were raised about 0.5 to 1 mm. above the level of the skin, the surface being flat or slightly convex, with definite papillary granulation. Inspection through a lens revealed a mamelonated wartlike appearance. The slightly adherent horny formations could be removed with a sharp knife, leaving in some instances papillary hemorrhages. The tessellation of the skin was normal. In places where the efflorescences extended beyond the finger joints they usually coincided with the folds, but in some instances they passed over even these. The skin of the hand appeared a trifle asphyxiated and the verrucous lesions slightly reddened, but under pressure with a glass spatula they appeared yellowish or brownish. The volar surfaces of the hand were entirely free, showing only slight induration, probably of occupational origin.

The nails on all the fingers were of an opaque, whitish, almost marble-like color, the normal areas appearing only as longitudinal reddish strips. The nails were infiltrated with air-filled striae and were extremely friable at the outer edge. The nail of the little finger was slightly atrophic and more involved than the rest. The nails on both index fingers showed paronychia. These changes were not typical and

1. Hopf, G.: Ueber eine bisher nicht beschriebene disseminierte Keratose (Akrokeratosis verruciformis), *Dermat. Ztschr.* **60**:227-250 (Feb.) 1931.

improbable for two main reasons: 1. The chemical nature of the eczematous sensitizers makes it unlikely that these substances could traverse any considerable amount of tissue without reacting. 2. A certain minimal concentration is required per unit of cutaneous area. There would not seem to be any reasonable explanation for this if the allergen itself were absorbed, for in this case one would think that the total amount would be the determining factor, whereas it is quite conceivable that in order to effect certain chemical interactions a requisite minimal concentration must be present. We are thus reduced to the conclusion that the eczematogenous allergen when applied to the epidermocutis reacts there to form a new compound allergen. The nature of this allergen is unknown, but the work of Landsteiner and Jacobs<sup>1</sup> and of Gell and his colleagues<sup>2</sup> make it appear likely that the new allergen is a protein conjugated with the simple chemical or with some derivative of it.

#### ROUTE BY WHICH THE COMPOUND ALLERGEN LEAVES THE SKIN

The question of the route by which the compound allergen leaves the skin has not been entirely settled but has been subjected to various experimental attacks with rather conflicting results. Landsteiner and Chase<sup>12</sup> endeavored to settle this question by making cutaneous islands in guinea pigs. Their technic consisted of isolating an area of epidermis so that its epidermal continuity had been severed and its continuity with the rest of the animal was via the blood vessels and the lymphatics, which run in the layer known in the guinea pig as the panniculus carnosus. (This layer overlies the superficial musculature.) If they applied their sensitizing allergen to the island and tested off the island they observed that the generalization of the sensitization depended on the integrity of the panniculus carnosus. If they cut through the panniculus carnosus the sensitization did not become generalized, whereas, if they did not cut the panniculus carnosus, it became generalized. Schnitzer,<sup>13</sup> in two studies on this point, was unable to corroborate these observations and noted that he did get generalization irrespective of whether or not he cut the panniculus carnosus. In some experiments which, however, differed in two important technical respects from the experiments of Landsteiner and Chase, I<sup>14</sup> observed that the cutting of the panniculus carnosus did not interfere with the generalization of sensitization.<sup>15</sup> These various experiments, while not settling the role

15. Rostenberg, A., Jr.: Studies on the Eczematous Sensitization: I. The Route by Which the Sensitization Generalizes, *J. Invest. Dermat.*, to be published.

16. It should be pointed out that in the technic of making a cutaneous island complete lymphatic isolation is not achieved even though the panniculus carnosus is cut, inasmuch as there are some lymphatics that communicate directly from the posterior surface of the island to deeper structures. The exact number of these lymphatics will depend on the size of the island and on its location.

resembled those observed in diverse keratotic processes on the hands. In this first case, the feet were normal and there was no hyperhidrosis.

Histologic examination revealed decided hyperkeratosis with horny cells in layers, although not to a pathologic degree. No intact nuclei were found in the stratum corneum. The papillae were frequently enlarged with slight acanthosis. The stratum lucidum was normal, but slightly enlarged. The individual cells were closely packed with keratohyaline granules. The prickle cell layer was somewhat denser in the acanthotic areas. The basal cell layer was perfectly normal. No vacuolation or cell degeneration could be demonstrated. Also the cutis appeared normal except for a slight increase of cells in the papillae. Especially in the perivascular areas there appeared a slight round cell and spindle cell infiltration. Connective tissue and elastic fibers were normal. The glands and their excretory ducts showed no change.

In Hopf's second case, the dorsa of both hands and feet were involved. Also in this case the disease had appeared about the time of puberty and had persisted unchanged since. This patient was 26 years old at the time of examination. No treatment had been successful. Her skin was otherwise normal except for slight seborrhea capitis. Numerous ephelides were observed on the face and chest. In this patient the eruption had more the appearance of irregular, gross plastering, like snake skin. The irregular network of normal skin on the dorsa of the hands corresponded fairly to the normal groove system. On closer inspection, the eruption on the dorsa of the hands appeared to be a dissemination of lentil-sized, some smaller, some larger, papular efflorescence, occasionally confluescing, especially at the ulnar sides of the hands, into large plaques. As a rule, these papules were sharply defined from the surrounding oval polygonal tessellation of the skin. Their surface was flat and slightly granular and on illumination showed faint but definite reflection. In this case also the palm was affected. At the level of the horny layer, papules on the volar surface could be noted and, in rare instances, fine pinhead-sized or pinpoint-sized horny pearls. Microscopic examination revealed interruption of the papillary ridges due to absence of some of the papillary elevations. This gave rise to numerous tiny pinhead-sized depressions, in some of which were tiny pearls. This appeared to be the mildest lesion, whereas the papular lentil-sized keratotic foci constituted the maximum intensity of the process. The lesions on the feet were like those on the hands, but harder and smoother, with a reflecting surface. There was a sharp line of demarcation toward the sole. The nails were intact, and there was no hyperhidrosis.

Rinsema<sup>2</sup> described a case of disseminated, macular keratodermia in a woman, whose brother showed involvement also of the dorsa of the

2. Rinsema, P. G.: Sur la kératodermie maculeuse disséminée symétrique, palmaire et plantaire (Buschke et Fischer), *Acta dermat.-venereol.* 6:299-304 (Oct. 25) 1925.

## EXISTENCE OF ANTIBODIES IN ECZEMATOUS SENSITIZATION

The existence of antibodies in eczematous sensitization is a point that has been much debated for a considerable number of years, and the bulk of opinion until very recently was that there were no humoral antibodies in this type of sensitization. It is well established that humoral antibodies of the nature of the Prausnitz-Küstner antibody are not present in eczematous sensitization. The specificity of the reaction, however, makes it likely that an antigen-antibody mechanism exists. It has been hypothesized that there were antibodies but that they were sessile and fixed to the epidermal cells and consequently could not be demonstrated in the circulation. Urbach and Koenigstein<sup>21</sup> conceived the idea that if one could damage these cells so as to liberate these antibodies and at the same time entrap them, it should be possible to demonstrate their existence. They therefore devised their cantharides technic, and they have claimed many successful transfers of epidermal sensitization by means of this technic. Recently, Landsteiner and Chase<sup>22</sup> succeeded in obtaining successful passive transfers by means of cellular exudates and bits of tissue obtained from lymph nodes and spleens of sensitized animals. It would thus appear that the sensitizing material is contained within the lymphocytes (and possibly other cells) and that when these sensitized lymphocytes are transported the sensitization is passively transferred. This may explain some of the successful Urbach-Koenigstein transfers, in that, fortuitously, a large number of cells were contained in the blister fluid, and these cells contained the sensitizing bodies. Further evidence for the existence of some sort of humoral sensitizing substance is contained in two experiments by Haxthausen.<sup>24</sup> The first experiment was made with 2 sets of identical twins, (1) A and B and (2) X and Y. A and X were sensitized to 2,4 dinitrochlorobenzene. An area of skin was interchanged between A and B and between X and Y, so that an area of skin from the sensitized A was in a nonsensitive B, and similarly for X and Y. After the grafts had taken, the subjects were tested both outside the grafted area and on the grafted area. In A there was a positive reaction both outside and inside the graft area, whereas in B there was no reaction outside or inside the graft area, and similarly

21. Cited by Urbach, E., and Gottlieb, P. M.: Allergy, ed. 2, New York, Grune & Stratton, Inc., 1946, p. 150.

22. Chase, M. W.: The Cellular Transfer of Cutaneous Hypersensitivity, J. Bact. 51:643, 1946. Landsteiner, K., and Chase, M. W.: Experiments on Transfer of Cutaneous Sensitivity to Simple Compounds, Proc. Soc. Exper. Biol. & Med. 49:688, 1942.

23. Footnote deleted by author.

24. Haxthausen, H.: The Pathogenesis of Allergic Eczema Elucidated by Transplantation Experiments on Identical Twins. Acta dermat.-venereol. 23:438, 1943; The Occurrence of Humoral Antibodies in Allergic Eczema Investigated Through Parabiosis Experiments on Guinea Pigs, ibid. 24:286, 1943.

study. Only 8 patients showed a normal titer at the latest follow-up examination. This result is similar to our observations in a study of the response of the serologic titer to the same three schedules of therapy in late latent syphilis.<sup>7c</sup> Of 143 patients with late latent syphilis treated with penicillin alone, the "8-6-3" schedule or the "5-12-3" schedule, only 1 patient succeeded in becoming normal.

#### COMMENT

Substantial improvement in the spinal fluid was noted in a majority of patients treated by each of the three methods used at the Center. Most of the improvement occurred during the first three month period immediately following treatment. Most rapid improvement was noted in the cell count and in the results of the colloidal mastic test, with changes in the total protein and in the results of the complement fixation test coming later and in lesser degree. These results are entirely in accord with previous reports on the treatment of neurosyphilis with penicillin. These changes are encouraging, but since they represent laboratory observations only, one should be careful not to attribute definite curative powers to penicillin in the treatment of neurosyphilis until adequate follow-up study lasting five years or more has demonstrated the absence of clinical evidence of the disease and also the permanence of the improvement in the spinal fluid.

Careful comparison of the results obtained using each of the three methods, penicillin alone, the "8-6-3" schedule and the "5-12-3" schedule, reveals a higher percentage of improvement in the spinal fluid with therapy combining arsenic, bismuth compound and penicillin. This difference, however, is not statistically significant because of the relatively small number of cases in this study, and it does not appear to be sufficient in degree to warrant exposing the patient to the additional risks of combined therapy. Experience in the treatment of large numbers of patients with early syphilis using the "8-6-3" regimen has disclosed a relatively high incidence of arsenical encephalopathy. It was the frequent occurrence of such conditions during 1945 that caused the United States Public Health Service to recommend the change to the "5-12-3" schedule, reducing the total dosage of arsenic and increasing the penicillin. Thus far, not many serious reactions have been reported as a result of "5-12-3" therapy. We have noted 1 instance of arsenical encephalopathy with this regimen at the Center in treating a patient with secondary syphilis. We do not feel that the added risk of the arsenic, however slight it may be, is justified by the slight difference in improvement in spinal fluid shown in this study by the combined form of therapy over therapy with penicillin alone.

We are of the opinion that a patient with asymptomatic neurosyphilis deserves a trial of at least one course, and probably several courses,

The lesions in the first patient had appeared at the age of 4 years, increasing in size up to her tenth year and then remaining stationary. The only other cutaneous manifestation was acne vulgaris. Both hands were affected, and the color of the lesions was more brownish than in the other cases and appeared more like snake skin. The eruption extended to the volar surface, where the lesions were not elevated. Owing to their transparency, they gave the impression of a pearly mosaic in the epidermis. Dactyoscopic pictures revealed numerous interruptions in the ridges. It would seem that this interruption in the ridges forms the basis for the development of the pearl-like formations. The dorsa of the feet were also affected but to a less degree. In the other 3 cases the lesions had been present since birth. Also the condition in Kren's case was congenital. Michael<sup>8</sup> described 3 cases with onset in the second and third decades. The histologic changes in his cases were similar to those described by Hopf, but some writers have regarded Michael's cases as atypical examples of cases of acrokeratosis verruciformis, owing to the late onset and the presence of larger papules in isolated groups rather than uniformly distributed over the dorsa. Michael considered the disease an acquired one, originating in the corium, with secondary changes in the epidermis. Attention has likewise been drawn to some histologic differences, as for instance the fact that the corium formed no wavy line of demarcation, the fact that parakeratosis was present and the fact that the rete pegs were long and thin, as in psoriasis. There may be an upward extension of the dermatosis, Hopf having described involvement of the palms, sole and face.

In 1935, Niels Danbolt<sup>9</sup> presented a series of 4 cases in one family in three generations. In this series the lesions represented a combination of Darier's disease with acrokeratosis verruciformis and Brauer's keratoma dissipatum in all 4 cases. The patients included a man of 21 years, his mother, his maternal grandfather and the grandfather's sister. Also in these cases onset occurred in early youth. In 1938 Lenartowicz<sup>10</sup> reported a case in an article entitled "Acrokeratosis Verruciformis Hopf"; however, the description corresponds to that of epidermodysplasia verruciformis of Lewandowsky and Lütz.<sup>11</sup> In 1940

8. Michael, J. C.: Discrete Keratoderma of the Dorsum of the Hands: A Probably Unrecognized Entity, Arch. Dermat. & Syph. **21**:215-227 (Feb.) 1930.

9. Danbolt, N.: Darier's sygdom kombinert med disseminat keratodermi på hender og føtter (Acrokeratosis verruciformis Hopf) og keratoma dissipatum (Brauer) i familiaer optreden i 3 generasjoner, Norsk mag. f. lægevidensk. **96**:246-258 (March) 1935.

10. Lenartowicz, J.: Acrokeratosis verruciformis Hopf, Zentralbl. f. Haut- u. Geschlechtskr. **58**:615, 1938.

11. Lewandowsky, F., and Lütz, W.: Ein Fall einer nicht beschriebenen Hauterkrankung (Epidermodysplasia verruciformis), Arch. f. Dermat. u. Syph. **141**:193-203, 1922.

and with bismuth. Follow-up examinations of spinal fluid in all these patients showed definite improvement in 69.6 per cent and normality in 25.1 per cent. Most of the improvement occurred in the first three months following therapy, and most rapid improvement was noted in the cell count and in the colloidal mastic test, followed by improvement in the level of total protein. The complement fixation test improved more slowly and to a lesser degree. Improvement in the serologic titer of the blood did not parallel improvement in the spinal fluid. In only 8 patients did the serologic test for syphilis turn normal. Results were slightly better after treatment with combined arsenic, bismuth compound, and penicillin than with penicillin alone. This difference does not appear to be statistically significant, and it is not sufficient to warrant the additional risks of combined therapy as contrasted with the safety of penicillin alone.

Further investigation and study are needed to establish the permanence of improvement in spinal fluid and the absence of clinical relapses following therapy with penicillin in neurosyphilis. Nevertheless, we feel that sufficient evidence is at hand to justify the treatment of asymptomatic neurosyphilis with at least one course, and preferably several courses, of penicillin before resorting to fever therapy.

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Kovacs<sup>12</sup> reported a case of Hopf's acrokeratosis verruciformis in a woman of 77 years, in whom the lesions on the dorsa of the hands and feet had been present since birth. Her father and 1 sister were likewise affected but not her mother and two other children. Histologic examination revealed acanthosis and severe hyperkeratosis with no degenerative changes. The lesions were diagnosed as Hopf's acrokeratosis verruciformis. In 1941 Loveman and Graham<sup>13</sup> described a case in a woman of 21 years whose mother had had a similar eruption since birth.

Owing to the obscure cause and numerous varieties of these eruptions observed, there has been no collective name for the hereditary palmoplantar keratoses. Moncorps<sup>14</sup> uses the term keratoses to designate all disease with a thickening of the horny layer, including idiopathic keratoses of the palms and soles. The forms appearing in multiple small foci are known as keratodermia. The latter may change during their course, completely retrogress or recur in a form different from the original lesion.

Since the real cause of the hereditary keratoses is not known, these lesions have been classified according to their clinical or pathologic features or on the basis of heredity. It has been demonstrated, however, that all stages of transition between various forms may be encountered and that hereditary factors may play a part also in the development of symptomatic keratoses. Recently Hopf has classified the manifold varieties of idiopathic keratoses of the palms and soles frequently seen in association with Darier's disease as nevoid lesions. There is a diffuse form, known as Unna-Thost disease, and a form appearing in multiple small foci.

It has been demonstrated that the idiopathic plantar and palmar keratoses may retrogress completely, to appear later in wholly different form. Possibly a morphologic classification will be found most suitable, including a disseminate, islet, striate and multiple foci form. Vohwinkel<sup>15</sup> used a classification according to localization, namely, palmo-plantar, knee-elbow and dorsa of the hands and feet, and drew attention to changes in the bones and motor apparatus associated with spontaneous amputations.

Moncorps<sup>14</sup> classified these lesions according to the clinical picture, time of onset and variations in the course. Various anomalies of kera-

12. Kovacs, S.: Ein Fall von Akrokeratosis verruciformis Hopf, *Dermatologica* **81**:6-11 (Jan.) 1940.

13. Loveman, A. B., and Graham, P. V.: Acrokeratosis Verruciformis (Hopf), *Arch. Dermat. & Syph.* **43**:971-979 (June) 1941.

14. Moncorps, C.: Palmoplantarkeratosen, in Jadassohn, J.: *Handbuch der Haut- und Geschlechtskrankheiten*, Berlin, Julius Springer, 1931, vol. 8, pt. 2, p. 300.

15. Vohwinkel, K. H.: Keratoma hereditarium mutilans, *Arch. f. Dermat. u. Syph.* **158**:354-364. 1929.

nodules, beginning at the base of the left thumb, on the dorsal surface, and extending up the flexor aspect of the forearm and the inner surface of the arm to just short of the axilla. These nodules ranged in size from 0.5 cm. to 2.5 cm. in diameter. They were not tender or painful. About half the lesions showed superficial necrosis and exuded a yellowish white, purulent fluid, while the others had not yet reached the suppurative stage. The axillary nodes were not enlarged. There were no constitutional symptoms.

*Laboratory Data.*—The microscopic and gross characteristics of cultures of purulent material and biopsy tissue grown on Sabouraud's dextrose agar at room temperature were characteristic of *Sporotrichum schenki*. The organism

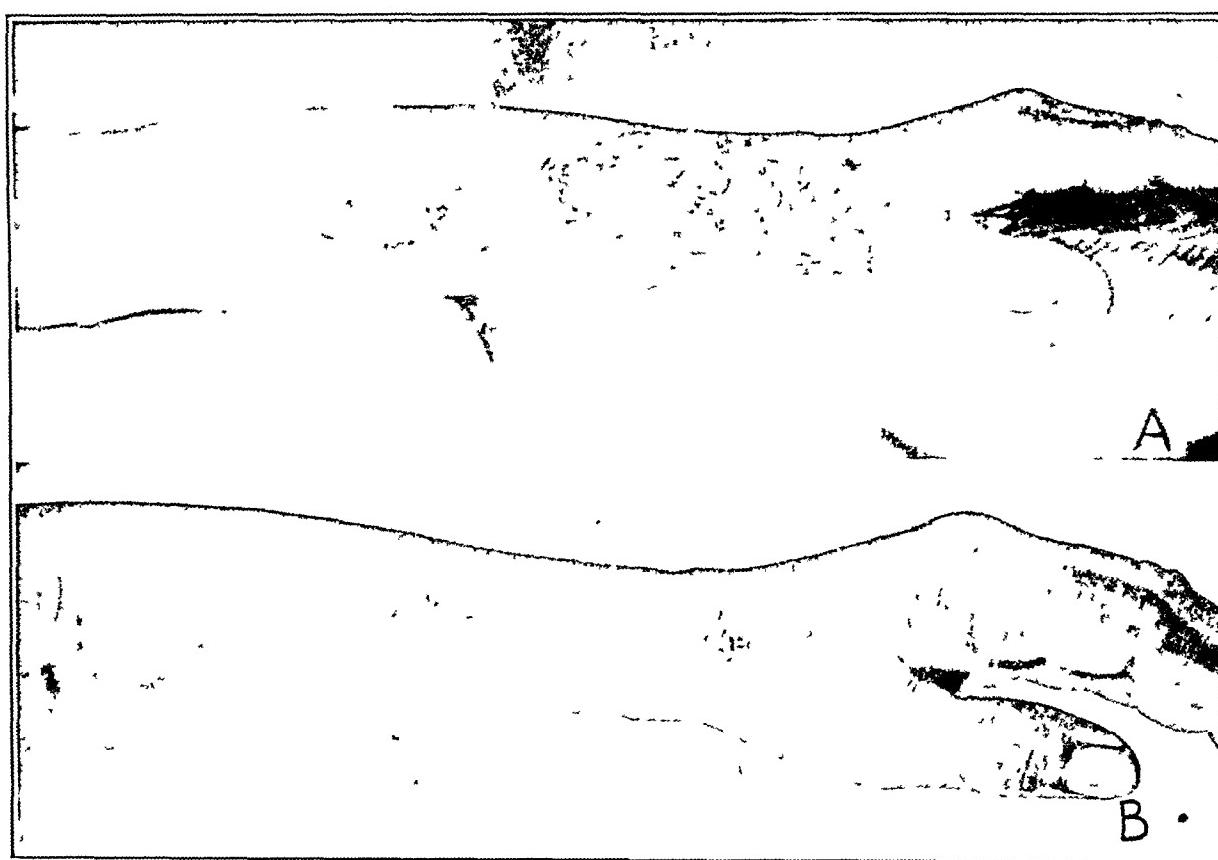


Fig. 1.—*A*, the patient's arm showing lesion of sporotrichosis before treatment; *B*, after eleven weeks of treatment.

was not demonstrated in direct smears. A blood count and examination of urine showed no abnormalities.

*Treatment.*—The patient was readmitted to Receiving Hospital on March 14 and given a course of sixty intramuscular injections of 20,000 units of penicillin every three hours for a total of 1,200,000 units. No clinical improvement was evident at any time during treatment or four weeks after penicillin therapy, and cultures were still positive for *S. schenki*.

On April 11 the iontophoretic treatments were begun. These were given daily Monday through Friday for a total of thirteen weeks. Strong solution of iodine, U.S.P., diluted 1 to 100 in isotonic solution of sodium chloride and increased to 1 to 50 after seven weeks was used. Ordinary toweling was moistened in the

tinization of hereditary origin may appear as diffuse, generalized lesions of the skin or a region-specific keratosis with special localization in the hands and feet. Differentiation of these eruptions is often difficult. In ichthyosis, for instance, there may occur localized eruptions on the hands and feet, while the cutaneous lesions elsewhere on the body may be insignificant and can be detected only after careful examination. The localized eruptions in ichthyosis may show peculiar clinical aspects difficult to distinguish from other keratotic anomalies of the soles and palms. Thus Thost first considered the disease affecting the soles and palms, later described by Unna as keratoma hereditarium palmare et plantare, as localized ichthyosis.

Also in Darier's disease, keratosis of the hands and feet may show a different clinical and histologic picture from the dyskeratotic papules elsewhere on the body. In some cases these hyperkeratoses seen on the palms and soles in Darier's disease may show a strong resemblance to the keratoses observed in patients suffering from ichthyosis.<sup>1</sup> The region-specific keratoses of the hands and feet appear in part as diffuse, macular or striate keratotic anomalies. Here, too, differentiation of the various types may be difficult, partly because the generalized dyskeratoses may have localized eruptions clinically resembling those of region-specific keratoses and partly because various congenital dyskeratoses have a tendency to appear in combination. Recognition of the different types will then require most careful examination of the initial efflorescence and its relation to the finer structural elements of the skin. This can be accomplished only by the methods devised by Betmann, the dermatogram and examination of the skin through the capillary microscope following staining with aniline dyes. Hopf has emphasized the frequent association of acrokeratosis verruciformis hereditaria with Brauer's disease (hereditary keratoma dissipatum), which he designates as acrokeratosis palmoplantaris disseminata.

As regards the simultaneous incidence of various forms of keratoses, lesions on the palms and soles have been described also in ichthyosis vulgaris universalis. In Darier's disease, there are sometimes lesions on the dorsa of the hands and feet, with interruption of the papillary ridges and small keratoses of the volar surface. Thorough microscopic and histologic study demonstrates identity with the changes seen in acrokeratosis and keratoma dissipatum. According to Hopf,<sup>16</sup> the disseminated keratoses appearing on the hands in Darier's disease are not characteristic dyskeratoses typical of Darier's disease but are a combination of Darier's disease with other region-specific forms of keratosis. The region-specific disseminated keratoses have the peculiarity of com-

16. Hopf, G.: Ueber die keratotische Destruktion der Papillarleisten bei den disseminierten palmo-plantaren Keratosen, Dermat. Ztschr. 65:12-24 (Nov.) 1932.

Pereyra<sup>3</sup> it is possible that an even more rapid effect could have been achieved had a wetting agent been added to the strong solution of iodine. The failure of treatment with penicillin in this case confirms the earlier experimental work of Keeney and his associates.<sup>4</sup>

#### SUMMARY

A case of sporotrichosis involving the left upper extremity showed complete healing after thirteen weeks of iontophoretic therapy with strong solution of iodine, U. S. P. There was no improvement after 1,200,000 units of penicillin had been given intramuscularly. In vitro studies demonstrated the failure of streptomycin to inhibit the growth of *Sporotrichum schenki*. The reaction to an intradermal test with an autogenous vaccine was strongly positive.

Norman F. Conant, Ph.D., Assistant Professor of Bacteriology, Duke University School of Medicine, confirmed the culture as *Sporotrichum schenki* and prepared the vaccine used in the intradermal tests.

C. W. Buggs, Ph.D., Assistant Professor of Bacteriology, Wayne University College of Medicine, made the in vitro studies with streptomycin.

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3. Pereyra, A. J.: Penetration of Surface Tissues with Copper by Iontophoresis, Arch. Dermat. & Syph. 52:96 (Aug.) 1945.

4. Keeney, E. L.; Ajello, L., and Lankford, E.: Studies on Common Pathogenic Fungi and on *Actinomyces Bovis*: III. In Vitro Effect of Penicillin, Bul Johns Hopkins Hosp. 75:410 (Dec.) 1944.

In the earlier days of treatment with colloidal gold its use was promptly halted whenever the leukocyte count dropped below 4,000 cells per cubic millimeter. Later a patient with a white blood cell count of 2,400 was given colloidal gold; the leukocyte count rose steadily to 5,000, and the sedimentation rate fell to a normal level. Clinical improvement was rapid. That colloidal gold sulfide seems to possess the added merit of not depressing the leukocyte count has been substantiated in all later cases.

Four persons with hypertension and albuminuria were treated in this series, and no harmful effects were observed. No toxic effects other than the occurrence of mild pruritus in a few patients were encountered. Damage to the liver, as reflected by an altered icteric index, was not detected. Little if any correlation between the clinical picture and the level of the leukocyte count or the sedimentation rate was noted.

The presence of itching in this disease has not been sufficiently emphasized. Fourteen patients complained of itching, and it was interesting to note that patients were usually relieved of this symptom after three or four injections. Of course, the relief from itching may have been due to the action of nicotinic acid.

In 1 patient with lupus erythematosus hypertrophicus et profundus disappearance of the raised border and the cribriform type of atrophy was observed.

The statement of Comroe<sup>8</sup> that colloidal gold preparations are therapeutically less effective in arthritis than are the crystalline salts of gold, probably because of insignificant gold concentrations in the plasma, apparently does not apply to cutaneous therapy. The level of gold in the plasma is obviously not an index of the curative power of gold.

Improvement in patients may be due solely to the change made from one gold compound, such as gold sodium thiosulfate, to another, such as colloidal gold sulfide. This has often been stressed as an explanation for the improvement observed whenever a change of therapy is instituted. However, the improvement noted in my series has been lasting, several patients having remained cured for as long as two and one-half years, so that such an explanation is not applicable here.

I am convinced that one cause of failure in the treatment of erythematous lupus in the past has been a hesitancy to administer large amounts of gold. Large doses must be given, and colloidal gold sulfide is apparently nontoxic even in large doses.

It is also my impression that patients who flush a good deal after taking nicotinic acid show the greatest amount of improvement. The minimal dose for the drug appears to be 100 mg. taken three times daily.

8. Comroe, B. I.: The Use and Abuse of Gold Therapy in Rheumatoid Arthritis, J. A. M. A. 128:848-851 (July 21) 1945.

vitamin A. Gradual improvement was reported by Peck in 9 cases of Darier's disease following oral administration of about 200,000 U. S. P. units of vitamin A daily.

In ichthyosis<sup>19</sup> the vitamin A level of the blood was found constantly below normal, but even following prolonged maintenance above the normal level no improvement in the clinical condition could be demonstrated. Peck<sup>20</sup> interpreted Darier's disease as a hereditary or acquired weakness in absorption of vitamin A or of conversion of pro-vitamin A to vitamin A, which reflects itself in the skin as a dyskeratosis.

In consideration of the varying time of onset and manifestations of these hereditary region-specific keratoses, a possible isomorphous hereditary or acquired increased susceptibility of these regions to toxins, angioneurotic influences and similar factors must be taken into account.

#### DIFFERENTIAL DIAGNOSIS

In characteristic cases diagnosis is easy, but atypical idiopathic keratosis may cause confusion. Unna-Thost diffuse keratodermia is often simulated by corneal thickenings due to physical factors, such as pressure, heat or external or internal chemical agents. One case of symmetric lesions on the dorsa of the hands of a child has been described as due to neurotic scratching. Also psoriasis, lichen planus, mycotic processes and tylotic eczema may cause confusion.

In the islet and striate types, diagnosis is based on idiopathic onset and familial incidence. In the extremely rare cases in which ichthyosis is limited to the palms and soles, diagnosis is likewise based on heredity. In erythrokeratosis involving the palms and soles, the progression of the disease and its appearance on other parts of the body are of aid in diagnosis. In rare cases disseminated or focal keratoses may follow infections, but these usually retrogress rapidly on recovery from the infection. In the symmetric keratoses of tabes, one may often find malum perforans. In cases of syphilids resembling multiple keratotic lesions, there are usually other symptoms of syphilis. In arsenic keratoses there are also diffuse or spotted melanoderma on other parts of the body.

The dorsa of the hands and feet may be involved in still another disease, namely, Meleda's disease<sup>21</sup> (keratosis palmoplantar trans-grediens). This is a special, atypical form of Unna's hereditary palmar

19. Peck, S.; Glick, A. W., and Chargin, L.: Vitamin A Studies in Cases of Ichthyosis, *Arch. Dermat. & Syph.* 48:32-34 (July) 1943.

20. Peck, S.; Glick, A. W.; Sobotka, H., and Chargin, L.: Vitamin A Studies in Cases of Keratosis Follicularis (Darier's Disease), *Arch. Dermat. & Syph.* 48:17-31 (July) 1943.

21. Niles, H. D., and Klumpf, M. M.: Mal de Meleda: Review of the Literature and Report of Four Cases, *Arch. Dermat. & Syph.* 39:409-421 (March) 1939.

clinical trial. The decided improvement in the accompanying leukopenia after the use of colloidal gold resembles our similar experience in a few cases in which we have used therapy with promin (sodium p,p'-diaminodiphenylsulfone-N,N'-didextrose sulfonate).

Although one must be cautious in evaluating the curative values of any medication, especially gold, in the treatment of this disease, in the light of our past experience, we feel this mode of therapy advanced by the presenter has definite merit and warrants future consideration in the treatment of this resistant disease.

DR. EDWARD A. OLIVER, Chicago: We are all confronted with cases of lupus erythematosus that do not respond to our customary treatment with gold sodium thiosulfate, with bismuth or with oxophenarsine hydrochloride. Most of these cases in which Dr. Schmidt has employed colloidal gold sulfide have been of that class. There have been several other cases, such as the cases of subacute disease that he mentioned, that do not fall into this category.

It was with the hope that some method might be devised whereby the gold would more effectively reach the spot that he began this treatment. I have seen and examined practically all these patients, and I can vouch for the statements that Dr. Schmidt has made as to their improvement. Most of them have shown steady but gradual improvement. There have not been any startling results, but I can say that my colleagues at Northwestern and I feel that the method is worth further trial.

Dr. Schmidt has brought out in his paper also the fact that the presence of severe leukopenia, hypertension or albuminuria in patients with lupus erythematosus is no contraindication to treatment with colloidal gold sulfide. That in itself is something that must be considered worth while, because we all know that in treatment with gold sodium thiosulfate we must stop the treatment time and again because of the leukopenia that develops. I still feel that this is only a beginning, and I hope that it will lead to further investigation by Dr. Schmidt. The only objection which I can see to the treatment at all, especially in dispensary work, is the fact that the preparation is not inexpensive; in fact, it is rather expensive. However, we felt that the greater expense of this preparation is worth while. I believe that Dr. Schmidt is going to continue with this treatment, and I wish him further success. I think that he has done a good job so far.

DR. ANTHONY C. CIPOLLARO, New York: Dr. Schmidt is to be congratulated and encouraged for giving to dermatology a new approach to the treatment of diseases—the physiologic approach. The use of vasodilators in the treatment of cutaneous disease is not new. The foreign literature has many articles referring to the use of vasodilators in the treatment of cutaneous diseases that are of dissimilar nature, varying anywhere from urticaria to lupus erythematosus.

Vasodilators are used much more by ophthalmologists, especially in the treatment of blindness due to tobacco, in which spectacular results are obtained if the blindness has not been present too long. The most practical vasodilator is sodium nitrite used intravenously several times a week, and vasodilatation can be maintained with the use of nicotinic acid in doses varying from 25 to 100 mg. three, four or five times a day, depending on the subjective symptoms of the patient. Erythrityl tetranitrate was used prior to nicotinic acid.

I would like to mention also that Dr. Eichenlaub at this meeting made a valuable contribution to this newer physiologic approach to the treatment of diseases and to the causation of cutaneous diseases. Many physicians have had experiences in which pruritic eruptions of various types were connected with some hepatic changes. For instance, I know of a case of a girl 13 years old with a primary carcinoma

Dr. Ayres brings up an interesting question which I will attempt to answer in a short time. He said that when one looks at a section of lupus erythematosus (at least that is the way I understood the question), vasodilatation is seen in the section; hence it is already there. What one sees is dilatation of the most peripheral blood vessels in the section, the smallest vessels, without seeing the larger arterioles which are constricted. When one considers the work of Lewis and of others, one finds that when histamine is released, it acts as a vasoconstrictor on the arterioles of the skin. In other words, the arterioles are constricted, but the end vessels become dilated. It is a peculiar phenomenon which has been described by Moon and by other pathologists at length. At first a little constriction of the capillaries is seen, but later wide open capillaries are seen as a compensatory result of the previous arteriolar constriction, the whole process ending in tissue anoxia because the circulation is sluggish through the end vessels.

is thicker and without appreciable infiltrate in the cutis. The nuclei of the vacuolated cells in epidermodysplasia, in contrast to those in verrucae planae, are shriveled and pyknotic. In both diseases a slight degree of parakeratosis is occasionally encountered. Lipschutz has noted similar changes in verruca vulgaris, and Kogoj has seen them in tuberculosis verrucosa cutis, carcinoma, molluscum contagiosum, senile keratosis, senile verruca, all types of warts, keratosis follicularis, keratoma hereditare palmare et plantare and Meleda's disease. In these diseases, however, the dysplasia is not so profound. Kogoj<sup>23b</sup> was of the opinion that vacuolar degeneration is common to all keratotic anomalies. According to him, Hoffmann and Gans, epidermodysplasia verruciformis is a special form of generalized disseminated verrucae.

In epidermodysplasia verruciformis there is a decided tendency to malignant transformation. The lesions may be disseminated, appearing on the face, neck and extremities, but are most prominent on the dorsa of the hands and feet. Lesions involving the lip and urethra have been reported. At times the lesions are confined to the dorsa of the hands. On the face the lesions resemble verrucae planae; on the trunk and extremities the lesions are larger and firmer, more like those of verruca vulgaris. The papules are flat topped, warty and lichenoid, rounded or polygonal and vary from grayish, dull pink to red-violet and brown. Other lesions resembling ephelides may be observed.

St. Deme<sup>24</sup> described a case of a man of 55 years in whom diffuse symmetric palmoplantar keratosis dating from childhood had been associated for twenty-five years with a tuberculosis verrucosa lesion on the sole of the right foot. Histologic examination revealed its true nature.

A peculiar feature described in some cases of acrokeratosis verruciformis is formation of blisters on slight injury. In Hopf's second case,<sup>6</sup> the patient complained of blisters, which she attributed to burns caused during her work as a laundress. However, later she noticed that the blisters occurred without relation to burns and could be induced by energetic rubbing but only in the region of the keratosis. The blisters developed several hours after friction and persisted for two to three days. Also 1 of the patients in Rehn's family of cases showed a tendency to have blisters develop.

This tendency has recently been described in Frank's dyskeratoid dermatosis.<sup>25</sup> In the latter, vesicles appeared one hour after production of a lesion by slight trauma, with a maximum reaction after three to five hours. This condition has likewise been interpreted as a nevoid

24. St. Deme: Ein durch das sekundäre Hinzutreten einer Tuberculosis verrucosa cutis deformierter Fall von diffuser Palmo-Plantarkeratose, *Dermatologica* 84:208-215, 1941.

25. Frank, S. B., and Rein, C. R.: Dyskeratoid Dermatoses, *Arch. Dermat. & Syph.* 45:129-147 (Jan.) 1942.

infections of the feet the patients were advised to dust the powder into their socks, or stockings, and shoes. Men were asked to change their socks daily and to disinfect them by boiling in soap and water for fifteen minutes. Women were advised to wear pads of cotton cloth covering their feet under their stockings. The pads were changed daily and disinfected by boiling. This precaution is useful because women's stockings made of silk, rayon or nylon cannot stand boiling. Patients with fungous involvement of the nails were instructed to scrape the nails thoroughly daily and then to rub in the ointment.

Several patients who had started the treatment and had discontinued it after the first or the second visit to the clinic were not included in this study. There remained 39 patients worthy of discussion. Thirty-four of them were analyzed as clinical entities. Five others presented combinations of fungous lesions with different localization and possibly different response to therapy; for instance, dermatophytosis and onychomycosis. These conditions were considered separate clinical entities, so that 39 patients presented 44 cases of mycosis for analysis.

The results of treatment were divided into (1) cure, (2) doubtful result and (3) failure. A patient was considered cured if a microscopic examination revealed no fungi and the skin became clinically normal. In some cases of dermatophytosis of the feet, however, it was impossible to bring the skin to an absolutely normal condition. Slight scaling or maceration, especially in the toe webs, persisted, even though microscopic examination did not reveal fungi. Such patients were also regarded as cured. The date of the first microscopic examination in which fungi were not seen was accepted as the date when the cure had been achieved, provided that there were no clinical or laboratory relapses. The result of the treatment was considered doubtful in spite of the microscopic examination if the clinical changes persisted to a considerable degree. The treatment was considered a failure if fungi were seen in microscopic examination regardless of the clinical improvement.

Table 1 gives a summary of all cases in regard to the clinical form, results of laboratory examination and results of treatment.

#### DERMATOPHYTOSIS OF THE FEET

Of 28 patients with dermatophytosis of the feet, 18 were registered as cured, 5 as doubtful and 5 as failures. Four patients were considered cured after a single microscopic examination did not reveal fungi. All these patients presented lesions on the soles. The infection in 3 patients cleared completely. The fourth patient showed a few scales when last seen, but the scales were free from fungi microscopically. Ten of the cured patients had two microscopic examinations in which fungi were absent. In 5 slight scaling of the toes was still noticeable.

In 5 patients with dermatophytosis of the feet, the result of treatment was considered doubtful. All these patients were free of fungi on one microscopic examination. They were not registered as cured, however, because the clinical changes still persisted when the patients were seen for the last time. The period of observation was from two to eight weeks. From 1 patient *T. interdigitale* was cultured and from the other patient *Trichophyton purpureum*.

In 5 patients the treatment failed to eradicate the infection. One of these patients showed fungi microscopically after two weeks of treatment but failed to return to the clinic. Two other patients, in 1 of whom the infection was due to *T. interdigitale* and in the other to *T. purpureum*, showed fungi in scrapings after three and one-half months of treatment. One of these 2 patients was not treated regularly. The fourth patient, who was infected with *T. interdigitale*, treated himself for six weeks, then discontinued treatment and came to the clinic two months later when fungi were seen microscopically. This

TABLE 2.—*Duration of Treatment Required for Cure of Dermatophytosis of the Feet*

Number of Weeks	Number of Cases
2.....	4
4.....	6
5.....	4
6.....	1
7.....	2
14.....	1

could possibly be a reinfection. The fifth patient had dermatophytosis of the toes and onychomycosis of the toe nails. Microscopic examination of the toe nails revealed a mixed infection with fungi of the ringworm type and the genus of *Monilia*. The toes on first examination showed only ringworm type of parasites. They cleared up and became microscopically free from fungi after three weeks of treatment. Four months later the toes were again infected. Fungi were observed microscopically and were eradicated after one month of treatment. Five months later the toes were reinfected, this time with *Monilia* fungi. In this case the treatment of dermatophytosis failed obviously because of repeated reinfection, first with ringworm fungi and later with fungi of the genus of *Monilia*, the reservoir of both parasites being present in the toe nails. Culturally only *T. interdigitale* was seen in the toes at the beginning of observation. Cultures from the nails were negative.

#### DERMATOPHYTOSIS OF THE HAND

Only 1 case of a true fungous infection of the hand (not an allergic eruption) was observed in a patient who also had dermatophytosis of the toes. The patient was cured of both in five weeks.

## ACNE VULGARIS IN TUBERCULOUS PATIENTS

A. W. STILLIANS, M.D.

CHICAGO

DERMATOLOGISTS generally agree that, with the exception of the orificial ulcer, tuberculous lesions of the skin are seldom seen in patients with active pulmonary tuberculosis. They occur more often in patients with latent foci and active cutaneous response to tuberculin. There are, however, two nontuberculous diseases of the skin, acne vulgaris and dermatitis seborrheica, which often accompany pulmonary tuberculosis. So often does this occur that acne has been suspected of having a tuberculous basis. Ramel<sup>1</sup> reported in 1930 that he had found acid-fast bacilli in material from acne lesions and by animal inoculation confirmed his suspicion that they were tubercle bacilli. He considered acne "an expression of a natural vaccination of the organism against tuberculosis." In the same year Griesbach<sup>2</sup> explained acne in the tuberculous as due to the exhaustion of the reticuloendothelial system by the toxins of tuberculosis, thus making the skin more susceptible to other organisms. By clinical investigation he determined that acne vulgaris was prevalent among those with phthisis, especially in those whose defense mechanism against tuberculosis was still rather efficient. In patients with severe pulmonary disease, whose resistance was overwhelmed by the toxins, acne was less common but, still, more frequent than in nontuberculous persons. He reported the incidence of acne vulgaris in 200 cases of pulmonary tuberculosis under his personal observation and in 3,015 such cases from the records of his sanatorium, the two groups corresponding closely in the percentage of acne cases. In 3,215 patients, 1,092 instances of acne were noted, about 34 per cent.

Several years ago I attempted a survey of the patients at the City of Chicago Municipal Tuberculosis Sanitarium to determine the prevalence of acne among them. I was not able to complete it, but I did obtain data on 400 female patients with active pulmonary disease. In classifying

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1. Ramel, E.: Acne vulgaire et tuberculose, Schweiz. med. Wochenschr. **60**: 754-760 (Aug. 9) 1930.

2. Griesbach, R.: Hautkrankheiten bei der Lungen tuberkulose mit besonderer Berücksichtigung der Akne, Ztschr. f. Tuberk. **57**:405-416, 1930.

Several patients noted relief from itching in a few days or one week. In some cases, however, itching persisted for five weeks.

*Resistance of Fungi to Treatment.*—On the basis of repeated microscopic examinations it can be said that fungi are capable of surviving a rather long period of treatment with undecylenic acid. In 3 of the cured patients fungi were still present in the scrapings after three weeks of treatment and in 1 other patient after six weeks. In 3 patients for whom the treatment failed fungi were seen microscopically three and one-half months after the beginning of the observation.

#### ONYCHOMYCOSIS

Of 4 cases of onychomycosis toe nails alone were involved in 3 cases, and toe nails and finger nails in 1 case. In 1 case, only one toe nail was affected. Fungi of the ringworm type were observed microscopically. This nail cleared up clinically and was twice observed to be microscopically clear, with a two month interval between the examinations. The first microscopic examination which did not reveal fungi was obtained six weeks after the beginning of the treatment. Such success in a case of onychomycosis, which is usually resistant to any therapy, was probably due to a rather superficial involvement of the nail plate.

In the second case of onychomycosis of one toe nail fungi were still observed microscopically three and one-half months after the beginning of the treatment. Six weeks later, however, fungi were absent on microscopic examination. The new growing nail looked much improved but not quite normal. The result of treatment in this case was considered doubtful.

In the 2 last-mentioned cases of onychomycosis the microscopic examination revealed the presence of a mixed infection with fungi of the ringworm type and of the genus of *Monilia*. In both cases the treatment failed. In 1 patient fungi were still present three months and in the other six months after the beginning of the treatment. Cultures were unsuccessful in all 4 cases of involvement of the nails.

#### MONILIASIS OF THE SKIN

In 2 patients fungi of the genus *Monilia* were observed microscopically and culturally. One patient with interdigital erosions on both hands was treated for four months. Her cutaneous lesions, although of a superficial type, showed no clinical improvement, and the scrapings continued to show fungi microscopically. The second patient with a paronychia of several fingers did not improve after five weeks of treatment. The microscopic examination was not repeated. In both cases the treatment was considered a failure.

ing them I have followed the plan of Bloch,<sup>3</sup> who graded them as follows: (1) those with less than five comedos, (2) those with from five to twenty comedos, (3) those with twenty to fifty comedos, papules and pustules and (4) those with more than fifty lesions. I shall report only on groups 2, 3 and 4, that is, acne in the narrower sense, hereafter called clinical acne, in order to compare my statistics with those of Hinrichsen and Ivy,<sup>4</sup> who reported the incidence of acne in three groups of otherwise healthy youths in the vicinity of Chicago. They found that in girls acne is most frequent at 17 and 18 years of age. They observed three groups: (1) boys and girls in a home for children, (2) boys and girls attending high school, and (3) young women attending the university. In their first group, 85.9 per cent of the girls had clinical acne, corresponding to Bloch's groups 2, 3 and 4. Of the second group, only 49.5 per cent of the girls had clinical acne, and of the third group, all women, only 47.5 per cent had acne of corresponding intensity. The difference between the incidence in the first and in the other two groups was due, the authors considered, to the preponderance in groups 2 and 3 of acne in the mildest form, which they explained as due to the better care given the skin by the members of these groups. As the patients in my series had ample opportunity to care for their skin, I believe that the fairest comparison is between them and groups 2 and 3 of Hinrichsen and Ivy.

The ages of greatest incidence of acne in my group were 17 to 26 inclusive. Of 163 patients within these age limits 129 had acne, a percentage of 79.1 against the 47.5 per cent of group 2 and the 49.5 per cent of group 3 cited by Hinrichsen and Ivy. Griesbach reported 513 cases of acne among 1,827 women with active pulmonary tuberculosis, a percentage of 28.1. No comparison can be made with his figures, for he gave no criterion by which he judged the presence or absence of acne.

In my opinion, a much more striking effect of infection with Koch's bacillus is the persistence of acne in the tuberculous patient beyond the age at which it commonly clears in the person who is not tuberculous. Bloch stated that acne is seldom seen after the thirtieth year. Loewenthal<sup>5</sup> in a recent article gave 13 to 25 as the ages of greatest incidence among the general population, stating that acne then declines in frequency and is seldom seen after 40. As I have said, in my group of women with phthisis the ages of greatest incidence were 17 to 26 inclusive, with acne in 79.1 per cent of the 163 patients. The decline in

3. Bloch, B.: Metabolism, Endocrine Glands and Skin Disease, with Special Reference to Acne Vulgaris and Xanthoma, *Brit. J. Dermat.* **43**:61-87 (Feb.) 1931.

4. Hinrichsen, J., and Ivy, A. C.: Incidence in the Chicago Region of Acne Vulgaris, *Arch. Dermat. & Syph.* **37**:975-982 (June) 1938.

5. Loewenthal, K.: Sensitivity to Tuberculin in Acne and Other Nontuberculous Diseases of the Skin, *Arch. Dermat. & Syph.* **47**:799-803 (June) 1943.

due to *Epidermophyton inguinale* while only 1 of 3 in whom the infection was due to *Trichophyton purpureum* was cured. Onychomycosis proved as resistant to undecylenic acid as to other chemicals. Only 1 patient of 4 was cured. In 2 patients with moniliasis (paronychia and interdigital erosions) the treatment failed. Pityriasis versicolor proved rather resistant to treatment. Four of 6 patients were cured in one to four weeks.

Undecylenic acid did not irritate the skin even in patients with acute vesicular and bullous eruptions. In fungicidal effect undecylenic acid was in general satisfactory but not superior to other chemicals used in the treatment of mycoses. However, the combination of a considerable fungicidal effect with a lack of irritation makes undecylenic acid valuable, especially in cases of acute inflammatory fungous eruptions and for patients with sensitive skins.

55 West Forty-Second Street.

frequency after 26 was slow. Between the ages of 27 and 50, of 174 patients, 63 per cent still had acne, and among 10 patients between the ages of 51 and 60 there were 4 in whom the acne still persisted. Thus it appeared that the presence in the body of active tuberculosis not only increased the frequency of acne but greatly prolonged its course.

While it seems that acne is made somewhat more severe by the presence of tuberculosis, so that it is not so easily controlled by the usual cosmetic procedures, I have not noted any great increase in severity among my patients. Of the 257 cases of acne there were only 4 that I could class as severe; none of them were of the deforming cystic type.

The influence of the menstrual cycle on acne in my patients and in persons without complicating general infection seemed parallel. If anything, there seemed to be less connection with the menses in tuberculous patients than in nontuberculous. On the other hand, several who suffered from aménorrhœa said that at the rare times when they did menstruate their acne became worse.

There is no doubt in my mind that the regimen of rest and full diet in the sanatorium contributes to the prevalence of acne as well as to the dermatitis seborrhœica frequently seen there. My survey, however, failed to show many affirmations of this belief. Only 7 of 56 patients in the second decade, after a stay of from one to forty-two months, acknowledged an increase of acne since they had entered. Of 108 patients in the third decade, residing in the sanatorium from one to one hundred and seventy-two months, only 26 stated that acne had grown worse after they had entered, while 2 reported improvement.

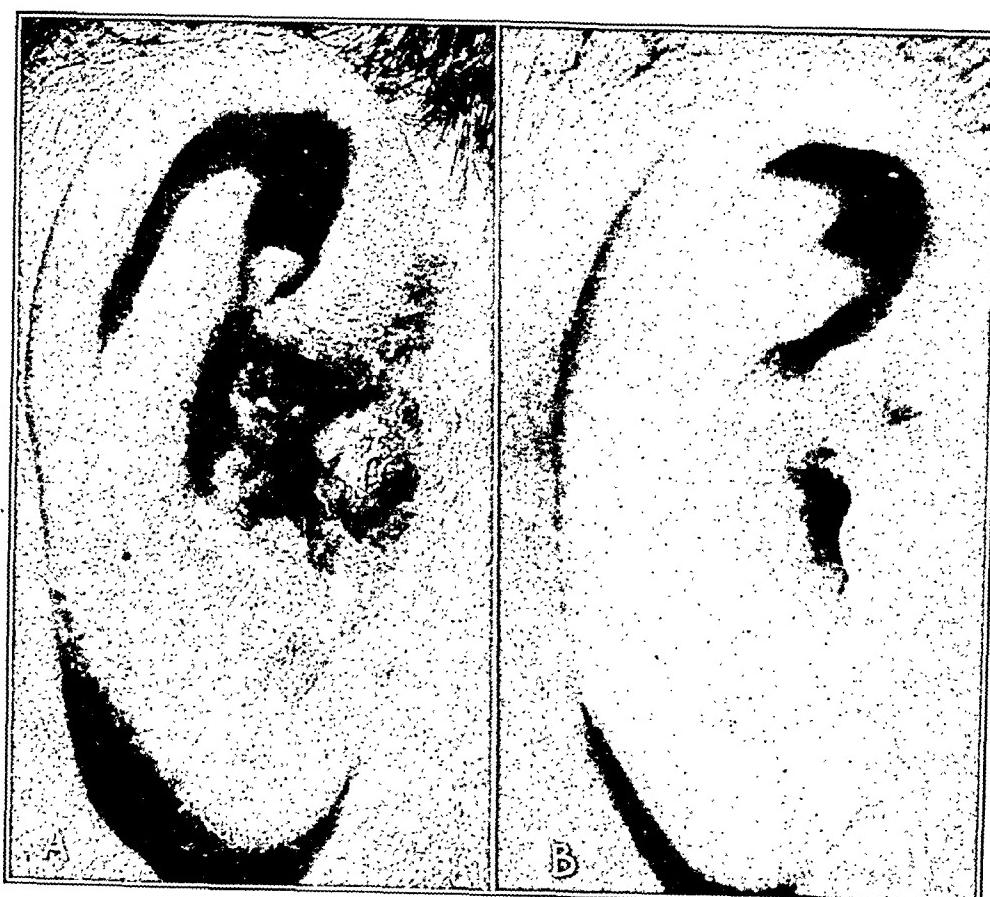
Griesbach's statement that he found more acne among the convalescents than among the very ill is corroborated by my figures. Of 177 infirmary patients 124 had acne, a percentage of 70. Among 67 convalescents in the cottages 58, or 86.3 per cent, had acne. I am assured that this is a significant difference which would occur by chance only 83 times in 10,000.<sup>6</sup>

The only occurrence of acne confined to one side of the back to come under my observation was in a man of 57, long a victim of phthisis. He said that his acne was of three months' duration, that it had always been confined to the right side of his back, and that he had never used oil or liniment on his back. There was only a sparse scattering of small papules and pustules on the left side of his back, but the right side was thickly studded with them. In three months this distribution did not change, but at the end of this time the acne had cleared under treatment with a sulfur preparation. Only then did I find mention of such a condi-

6. Figures are from Dr. F. T. Jung, Associate Professor of Physiology at Northwestern University Medical School.

external canal of the right ear (figure, A). The surrounding tissue was swollen, red and indurated. Unilateral lymphadenopathy was present on the right side of the neck and below the right ear lobe. A fine macular rash was noted on the chest and back. Dark field examinations were performed on several occasions, and they revealed numerous *Treponema pallidum* organisms per field. Serologic tests for syphilis revealed a positive Kahn reaction with 20 Kahn units and a positive Wassermann reaction. Several serologic tests of the blood were performed, all of which gave strongly positive reactions.

The lesion of the ear was not typical of a chancre, because it had been distorted by previous removal of a biopsy specimen and because it was secondarily infected. However, it had a granulomatous base.



A, chancre of the ear. B, chancre after four days of treatment with 2,400,000 units of penicillin.

A diagnosis of a primary chancre of the ear was made because of the following factors: (1) history of several exposures to "pick-ups" during the latter part of April and the early part of May 1945; (2) previous negative serologic reactions of the blood for syphilis; (3) dark field examinations positive for *Treponema pallidum* on several occasions; (4) repeated positive Wassermann and Kahn reactions (a quantitative Kahn test gave a positive reaction with 20 units), and, (5) a macular rash on the chest and back.

*Treatment.*—The patient was given intensive penicillin therapy, consisting of sixty consecutive intramuscular injections of 40,000 units each at three hour intervals, for a total dose of 2,400,000 units. He had both a focal and a systemic

## Clinical Notes

### TRICHONODOSIS

#### Report of a Case

A. G. PRATT, M.D., CAMDEN, N. J.

Trichonodosis, or knotted hair, is described briefly by McCarthy.<sup>1</sup> He mentions two types. One variety, rarely seen, occurs as a solitary knot associated with abnormal growth of the hair. The second type is commoner, according to the European authors<sup>2</sup> cited by McCarthy. This variety occurs as multiple knots and probably results from physical and mechanical forces such as combing, singeing, washing and the habit of running the fingers through the hair.

McCarthy stated in 1940 that there are no reports of this condition in the American literature. The "Quarterly Cumulative Index Medicus" for the years 1939 to 1945, inclusive, contains no American references and only one foreign reference.<sup>3</sup> The index of *The Journal of the American Medical Association* for 1946 and the index of the *Current List of Medical Literature of the Army Medical Library* for 1946 contain no references to trichonodosis.

In addition to McCarthy's chapter the subject is mentioned in the texts of other American authors<sup>4</sup> on the basis of the European articles. The Suttons illustrate their article with a photograph of multiple knotted hairs supplied by F. Ronchese of Providence, R. I.

The following report deals with the solitary knot type of trichonodosis.

#### REPORT OF A CASE

J. DiN., a 25 year old woman of Italian parentage, was first seen Nov. 1, 1945 because of loss of hair of three years' duration. The loss started gradually and was continuous.

The scalp was clean, though with a small amount of loose white scale. The most prominent feature of the scalp was the diffuse partial alopecia at the frontal area and at the vertex. Here the remaining hairs were dry, dull appearing and short, varying from 2 to 10 cm. in length. The hairs in the parietal and occipital areas of the scalp were longer, up to 20 cm. in length, but likewise dull and dry.

1. McCarthy, L.: Diseases of the Hair, St. Louis, C. V. Mosby Company, 1940, pp. 103-104.
2. Westphalen, V.: Ueber einige Haarerkrankungen, Leipzig, J. A. Barth, 1884, vol. 19.
3. Kren, O.: Ueber das Vorkommen der Trichonodosis, Wien. klin. Wchnschr. 20:916, 1907.
3. Cajkovac, S.: Morphology and Pathogenesis of Trichonodosis, Liječn. vjes. 61:471, 1939.
4. Pusey, W. A.: Principles and Practice of Dermatology, New York, D. Appleton & Company, 1911, p. 986. Ormsby, O. S., and Montgomery, H.: Diseases of the Skin, Philadelphia, Lea & Febiger, 1943, pp. 1248-1249. Sutton, R. L., and Sutton, R. L., Jr.: Diseases of the Skin, St. Louis, C. V. Mosby Company, 1939, p. 1312.

group the patients with acne responded to intracutaneous tuberculin tests much as did the controls. In the older group, however, the controls showed a decided increase of sensitivity to tuberculin, which was not manifested by the patients with acne. If it is found that the older patients without acne regularly show increased sensitivity to tuberculin which does not develop in the older patients with acne, this failure may in some cases signify an inability to build up resistance to tuberculosis. These persons when exposed to infection fall easy prey to tuberculosis and thus form a large element among the victims of the "white plague."

Though there may seem to be some relationship between acne and the ability to resist tuberculosis, I cannot believe that acne is an expression of allergy in any of its phases. Variations in resistance to infection seem to affect acne, but it is my belief that chemical and physical changes in the sebum, brought about by endocrine influence and increased by neglect of cleanliness, by unwise diets, even, in some cases, by foods that indirectly influence the sebum, by drugs of the halogen group and by external contact with oil, tar or chlorine, are of much greater significance in explaining this common malady. A devastating infection like tuberculosis alters many bodily functions and may modify the sebum, increasing and perpetuating the irritation caused by it.

104 South Michigan Avenue.

#### ABSTRACT OF DISCUSSION

DR. EDWARD A. OLIVER, Chicago: Dr. Stillians is to be congratulated on having been able to study 400 cases of acne in a tuberculosis sanatorium. His paper is full of interesting facts. I venture to state that not many of us were aware of the fact that acne vulgaris is prevalent among those suffering with tuberculosis, nor were we aware that acne is not so prevalent among the seriously ill with tuberculosis but yet more prevalent than among persons who do not have tuberculosis. His figures showing 129 cases among 163 patients in the 17 to 26 year group are amazing, and still more so is the fact that of his 174 patients between the ages of 27 and 50, 63 per cent still had acne.

It would certainly seem that the presence of active tuberculosis not only increases the frequency of acne but also prolongs its course. On first thought, we might say, of course, that the disease is more prevalent in tuberculous patients because they are generally fed a diet rich in carbohydrates, they do not get exercise, and, also, I would feel that they do not take as good care of their skin as they would if they were well. But then we learned that these patients had acne before entering the sanatorium, that they did not get worse after months of life in the sanatorium, nor did they get better. This is difficult to explain. Dr. Stillians also shows that during periods of fever, when one would think that it would improve, the acne became worse.

Dr. Stillians emphasized the fact that those who were very ill showed a less severe type of acne, which is difficult to explain. One would suppose that because of their feeble resistance they would have a much more serious type of disease. The reverse seems to be true.

"Dear Doctor: Having seen your article in the March number of the *Journal of Cutaneous and Genito-Urinary Diseases* on the subject of the "Cutaneous Punch," I wish to call your attention to the fact that an instrument for the same purpose and of similar construction was used by me in 1877 and was fully described in two articles published, one in the *New York Medical Record*, July 27, 1878, page 78, entitled "Discotome" and the other in the *St. Louis Medical and Surgical Journal*, Vol. XXXV, page 145, entitled 'Gunpowder Disfigurements.'

"Yours sincerely,

"B. A. Watson."

"To the Editor of the *Journal of Cutaneous and Genito-Urinary Diseases*:—  
"Dear Doctor: I am entirely unconscious of ever having seen either of the articles referred to above, but it is only just to Dr. Watson that he should have the credit of priority if he wishes it, and the publication in your Journal of this letter with mine will give it to him.

"Yours very truly,

"E. L. Keyes."

Is it not curious, though, that sixty years later the punch is almost always referred to as the Keyes punch?

18 East Eighty-Ninth Street.

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#### CAUTERY DRAINAGE OF SUBUNGUAL ABSCESS

THOMAS S. SAUNDERS, M.D., PORTLAND, ORE.

Collections of pus under the nail plate can be satisfactorily opened and drained, without anesthesia, by applying a small heated cautery tip<sup>1</sup> to the portion of the nail overlying the pus. In an instant, a small opening is formed and the pus escapes. The immediate relief of pain is gratifying.

This procedure is a modification of that used by a colleague, Dr. R. E. L. Holt, for the treatment of subungual hematoma. He heats a small wire (piece of paper clip) to white heat and burns an opening in the nail plate, releasing the blood.

In some instances cautery drainage of subungual abscess will not suffice. Cure will be obtained in such cases only by removal of a portion of or the entire nail.

1020 Southwest Taylor Street.

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1. Number 3 cautery tip, National Electric Instrument Co., Long Island, N. Y.

York, established a foundation the purpose of which is to assist medical schools in improving the undergraduate and graduate instruction in psychiatry. The association proposes to assist in the selection of teachers when vacancies occur, to outline an adequate curriculum in the teaching of mental diseases and to offer advice in general to the medical schools on all subjects pertaining to psychiatry.

The specialty of dermatology also needs such a foundation. The important representative societies must sponsor such a movement. We must be the aggressors in securing for dermatology a better position in our schools and in the medical departments of the armed forces.

The passing generation of practitioner teachers need the help of and eventually will be supplanted by selected young men who are trained and suited for and willing to elect an academic career in dermatology. The medical faculties must furnish them with the material with which they may teach, do fundamental research and thus advance our knowledge of cutaneous medicine.

It is urged that the officers of our various societies consider the establishment of a dermatologic foundation, and it is earnestly hoped that in this endeavor they will receive the support of all dermatologists and medical faculties in securing for the specialty the facilities and the place in our system of medical education which its attainments and its future deserve.

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## Current Comment

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### ANNUAL MEETINGS

The annual meetings of the American Dermatological Association, Inc., the Society for Investigative Dermatology and the Section on Dermatology and Syphilology of the American Medical Association held June 1947 were notable events in many respects. They were unusually well attended, and the papers, which in general indicated careful preparation, were practical and interesting and stimulated thoughtful discussions. The subjects were extensive and diversified and included almost all aspects of dermatology. There were discussions devoted to the newer field of geriatric dermatoses, cutaneous reactions to systemic disease, new drugs, new treatments for familiar diseases, new laboratory investigations, problems of nosology and even problems of training in dermatology. The advisability of holding an international congress of dermatologists in the near future was also discussed informally.

Dermatology participated actively in the eminently successful centennial celebration of the American Medical Association. The achieve-

## CUTANEOUS MANIFESTATIONS OF MONOCYTIC LEUKEMIA

W. R. HUBLER, M.D.

YOUNGSTOWN, OHIO

AND

E. W. NETHERTON, M.D.

CLEVELAND

THE PURPOSE of this study is to review 50 cases of monocytic leukemia of the Schilling type which have been observed at Cleveland Clinic Foundation Hospital since 1933. The majority of the patients were admitted to the medical service of Dr. Russell Haden, who made the hematologic diagnosis of monocytic leukemia in all cases. Histopathologic changes in cutaneous lesions of the specific type were studied in selected cases. The symptoms and clinical course of the disease are discussed briefly, and special consideration is given to the incidence and characteristics of cutaneous lesions observed. Detailed discussion of the hematology, which properly belongs in the province of a hematologist, was considered to be beyond the scope of this study. Suffice it to state that careful hematologic studies were made in each case.

Previous observers have emphasized that certain types of mucocutaneous lesions occur often in monocytic leukemia than in the lymphatic or myelogenous types. However, none of the lesions are pathognomonic, and the differential diagnosis of leukemias is ultimately dependent on the hemogram. Therefore, in the study and classification of leukemia cutis and other lymphoblastomas, it is essential for the dermatologist to have the cooperation of a competent hematologist and pathologist.

The cutaneous lesions of leukemia are of two types: (1) specific, consisting of papules, nodules and plaques, in which there is leukemic infiltration of the skin and subcutaneous tissues (a pyogenic process may involve specific lesions, with resultant ulceration), and (2) non-specific, such as purpura, furuncles, carbuncles or toxic erythematous vesicular, bullous or pruritic papular eruptions, in which leukemic infiltration does not occur.

In this series of cases monocytic leukemia was an acute disease. It usually became manifest by rapidly progressing weakness, anemia and septic fever. Sore throat and swollen, bleeding gums were common

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Dr. Netherton is from the Cleveland Clinic.

Read at the Section on Dermatology and Syphilology of the Ninety-Fifth Annual Session of the American Medical Association, San Francisco, July 5, 1946.

## Society Transactions

### MANHATTAN DERMATOLOGIC SOCIETY

E. W. Abramowitz, M.D., President

Wilbert Sachs, M.D., Secretary

Nov. 13, 1945

#### Erythema Annulare Centrifugum. Presented by DR. JACK WOLF.

E. H., a man aged 53, is presented from the Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital with an eruption on the back and abdomen of five months' duration. He gives no history of ingestion of drugs.

The lesions are of gyrate, circinate and annular configuration, ranging from 5 to 10 cm. in diameter. The borders of the lesions are raised, pink, firm and smooth; the centers are clear.

The eruption has improved somewhat with weekly injections of bismuth subsalicylate.

#### DISCUSSION

DR. DAVID BLOOM: The lesions are not annular but serpiginous, and some are circinate. Bismuth therapy is indicated in these cases.

DR. EUGENE F. TRAUB (by invitation): While I have seen improvement with injections of a bismuth preparation, the results do not compare with those of irradiation with small doses of cold quartz-mercury vapor light. Not infrequently one treatment will result in the disappearance of a fixed patch of erythema which has been present for months or years. Unfortunately, the eruption has a tendency to return, so that the combination of bismuth therapy and cold quartz-mercury vapor irradiation is better than either alone. Why the eruption should disappear so promptly after exposure to the cold quartz-mercury vapor radiation I do not know.

DR. SAMUEL M. PECK: I get the impression that this disorder is unusually prevalent. I have never seen so many cases at one time, both in hospital and in private practice. It is almost like an epidemic.

DR. GEORGE C. ANDREWS: I agree that this disease is unusually prevalent. I have 2 patients now under my care, more than I have had in years. I wonder whether any one has tried the sulfonamide drugs or penicillin in the treatment of this disease.

DR. MIHRAN B. PAROUNAGIAN: I suggest that the kidneys be thoroughly examined. I recall a case at Bellevue Hospital, that of a man who had somewhat more pronounced lesions, with elevated borders; the eruption looked like erythema multiforme. He died of a renal disease, and autopsy showed that the kidneys were full of pus. I believe the kidneys were the cause of the cutaneous eruption.

DR. GEORGE C. ANDREWS: In the literature many varieties are described.

DR. DAVID BLOOM: The variety of erythema annulare centrifugum described by Lipschütz differs from that described by Darier chiefly in the number of lesions. There is no essential difference between these two types.

DR. E. W. ABRAMOWITZ: Although the case is fairly typical, there should be an examination for fungi. I have been surprised at the response of this eruption to injections of bismuth subsalicylate. The eruption returns, however, and the treatment has to be repeated.

DR. JACK WOLF: In erythema chronicum migrans (Lipschütz) one finds a single lesion extending peripherally, which does not form gyrate lesions and does not break up into numerous lesions; it remains single. Whereas numerous lesions

**Lupus Erythematosus.** Presented by DR. MAX SCHEER.

C. P., a woman aged 36, is presented from the Skin and Cancer Unit of the New York Post-Graduate Hospital with an eruption on the face of two years' duration.

The eruption covers the entire face in masklike fashion, sparing the eyelids and the alae of the nose. The lesions are confluent, flat, indurated and bright red. Telangiectasis; small, yellowish, adherent scales, and dilated follicles are present.

The patient states that this eruption appeared during the time she was employed as a welder, using a blowtorch, which produces a continuous ultraviolet flash.

The histologic picture confirms the clinical diagnosis of lupus erythematosus.

**DISCUSSION**

DR. HERMAN SHARLIT: I should like to ask whether lupus erythematosus is a recognized hazard of the welding industry. A certain amount of protection is to be had from goggles.

DR. SAMUEL M. PECK: That industry knows the hazard well and takes good care of its people. I have never been in a plant where workers did not have some protection. I asked the patient whether she was a welder's helper, for the helper wears only goggles and is therefore the one who gets the maximum exposure: The welder himself wears heavy canvas gloves, an apron and a plastic hood extending well down on the chest.

DR. GEORGE C. ANDREWS: One other question comes to mind. What was the patient's diet and state of nutrition before this actinic exposure?

DR. MIHRAN B. PAROUNAGIAN: I agree with the diagnosis. A number of cases of lupus erythematosus have occurred on exposure to sunlight.

DR. SAMUEL M. PECK: The patient says that her welding was performed with a blowtorch. I think it is important to state in the record just what she was doing. This case would be the first I have heard of in which the eruption could be traced to ultraviolet light from a welding arc.

DR. EUGENE F. TRAUB: Dr. George M. Lewis showed a case at a meeting of the New York Dermatological Society in which a similar sequence of events was said to have occurred, but there was the same question of protection. These welders frequently work on the decks of ships or out of doors; they may take off their masks and get a natural sunburn, and the welding may not be a factor at all.

DR. ANTHONY C. CIPOLLARO: It is a question in my mind whether welding has anything to do with lupus erythematosus. I think this patient has lupus erythematosus, and if welding has anything to do with it, this factor should furnish a clue to the cause of lupus erythematosus. The consensus now is that lupus erythematosus is of infectious, rather than actinic, origin.

DR. HERMAN SHARLIT: You do not believe that actinic rays have anything to do with precipitating the eruption?

DR. ANTHONY C. CIPOLLARO: Actinic rays might be a precipitating or an additive cause, but I feel that lupus erythematosus is of infectious origin.

DR. DAVID BLOOM: Was the patient exposed to much heat during her work as a welder?

DR. E. W. ABRAMOWITZ: Lupus erythematosus has been reported in the literature as occurring after burns and other injuries. The Viennese school particularly, and I believe the French school too, still believe that lupus erythematosus of the discoid type is of tuberculous origin in most cases. However, the incidence of tuberculosis in Europe renders judgment on that point difficult. The English and Americans believe that some other cause is operative in most cases of lupus erythematosus. This patient has lupus erythematosus. It might be difficult to disprove that her occupation was not causally related to her eruption.

never present in increased numbers in patients with myelogenous and lymphatic leukemia.

In all cases in this series the monocytic leukemia was of the Schilling type. Studies of the blood made on 27 of our patients on the first visit showed only anemia of varying severity and moderate or no leukocytosis, but in smears of the blood the differential count showed an increase in mature monocytes of over 23 per cent. On the initial count in 10 cases immature monocytes or monoblasts were present in large numbers. In all cases possible, studies of the blood were made at weekly intervals throughout the patient's stay in the hospital and subsequent visits. Of the 27 patients having only a relative or actual monocytosis on the first visit, 16 had simultaneous studies of the bone marrow demonstrating decided increases in the monocyte series. Subsequent studies of the blood revealed many immature cells of the monocyte series.

Studies of the sternal bone marrow are of considerable diagnostic and confirmatory value and should be performed in each suspected case, as it may be days or weeks before diagnostic immature cells of the monocyte series appear in the peripheral blood stream.

Watkins and Hall<sup>8</sup> attempted to differentiate the two types of monocytic leukemia on the basis of studies of the bone marrow. In a review of 30 cases seen at the Mayo Clinic from 1929 to 1939, they stated that the bone marrow in the Naegeli type showed myeloblastic hyperplasia but no change in the reticulum or reticular cells. In the Schilling type the bone marrow was also hyperplastic but consisted of young and mature monocytes and, in addition, showed reticular hyperplasia. Transition of the reticulum cells into young monocytes could be demonstrated by them.

Specimens of bone marrow were obtained from 20 of our patients. Most of these showed monoblastic or monocytic predominance and depression of the myeloid series. An increase in reticulum was also noted. Initial studies of the bone marrow were diagnostic in all but 5 cases. In 4 of these the picture of the peripheral blood showed either an abnormally high percentage of monocytes or many identifiable young cells of the monocyte series.

The total white blood cell count on the patient's initial visit was below 4,000 in 30 per cent of our cases. Twenty-six per cent had white cell counts within 4,000 to 11,000 and 44 per cent above 11,000. The extremes were 350 and 233,000 white cells. None of the more than 20 patients on whom we were able to obtain repeated hemograms until death showed any evidence of reversion to myelogenous leukemia, and in most cases the leukocytosis remained moderate, even though the white cells became more primitive.

8. Watkins, C. H., and Hall, B. E.: Monocytic Leukemia of Naegeli and Schilling Types, Am. J. Clin. Path. 10:387-396 (June) 1940.

across the lip and connecting with the epithelium of the mucous membrane of the oral surface of the lip. The tumor was composed of multiple, irregular nests, both small and large, of well differentiated, often keratinizing, squamous cells, with a few mitotic figures. The surface was highly irregular, with projections and depressions, and was filled with keratin. There were extensive fibrosis and diffuse chronic inflammation around the infiltrating tumor. The growth did not reach the planes of surgical excision at any point and appeared locally to have been completely excised.

The patient was advised to return to the hospital two weeks later for a dissection of the neck.

#### DISCUSSION

DR. HERMAN SHARLIT: It is interesting to what extent one can feel satisfied with the supposition that injury played a real and effective part in the genesis of this tumor; on the other hand, one wonders whether an accident which occurred several weeks before was not just coincidental. Can injury produce cancer? The man is convinced that he received a severe injury in that exact location and that a fulminating cancer developed within a short time.

DR. GEORGE C. ANDREWS: From all that I have read or been taught by Dr. James Ewing or Dr. Francis Carter Wood, I have always been of the opinion that trauma is seldom the cause of carcinoma. It may be a cause of some sarcomas. However, chemical irritation frequently seems to favor the growth of cancer. It is possible, of course, that ideas have changed in the past few years, but I had not heard of it. Dr. Wolf says that the role of trauma was accepted in his cases. Will he tell us who accepted the traumatic origin?

DR. JACK WOLF: It is always difficult, if not altogether impossible, to establish causal relations in a rapidly growing lesion. There have now been enough reliable reports of cases which have followed an acute injury to leave little doubt that acute injury may occasionally cause cancer. I have 2 personal cases in mind, 1 in which a piece of metal was lodged subcutaneously over the bridge of the nose, with a basal cell epithelioma developing in the course of the next few months at the site of injury, and another in which a basal cell epithelioma of the cheek followed a burn produced by a hot "scale."

DR. MIHRAN B. PAROUNAGIAN: I have always understood that trauma was the cause of cancer in a considerable number of cases. Not long ago I saw a man who cut himself with a razor blade on the malar process, as a result of which he presented a definite cancerous lesion.

DR. ISADORE ROSEN: There is something unusual and striking about the lesions. If I knew nothing of the history, I should undoubtedly make a diagnosis of multiple gumma. I feel that it would be advisable to treat this patient with three or four intramuscular injections of bismuth subsalicylate 10 per cent emulsion in peanut oil and oral administration of potassium iodide before more radical surgical procedures are instituted.

DR. ANTHONY C. CIOPOLLA: I should like to elaborate on the statement that chemical trauma may have something to do with cancer and, in support of that idea, to cite the case of a man with an epithelioma of the lower lip. He also had syphilis and was treated for two or three weeks with arsenicals, by which time the lesion had become four to six times as large as it originally was. Most of the men who saw this patient thought arsenic had something to do with the rapid growth.

DR. SAMUEL B. PECK: I think we ought to bring up for discussion this question of the relation of trauma to carcinogenesis. Throughout all industries one has definite proof that certain of the coal tar products and certain of the petroleum hydrocarbon products will cause cancer. Certain industrial methods are known to produce carcinoma of the bladder, so that all workers are required to have cystoscopic examinations at intervals. It is not so much the irritation which is responsible for cancer as a specific effect, probably due to a definite chemical structure.

## DISCUSSION

DR. H. HECHT: This disease is rare in the United States. Years ago I saw a few cases in Prague. The microscopic picture was typical. I remember 2 cases in which the larynx was infiltrated. Treatment is not satisfactory. One may remove the lesion surgically or try roentgen therapy.

DR. R. E. BARNEY: Had there been a lesion on the other side of the lip, involving the mucous membrane of the left naris? There was a small area on the upper lip which looked like the scar of a surgical incision. Had a process been present and healed?

DR. W. W. MURPHY: So far as we have been able to learn, the lesion on the right side is the original and only one. The growth first appeared about two years ago, when the patient was sent to City Hospital from Cleveland State Hospital. At that time it was described as a small, wartlike lesion. Over the intervening period it has developed to its present size.

DR. E. W. NETHERTON: Rhinoscleroma is described as hard, firm and woody, features absent in this case. Is this common?

DR. H. HECHT: Most such lesions are very hard.

DR. W. W. MURPHY: Cunningham and Guerry (Scleroma, *Arch. Otolaryng.* **36**:662 [Nov.] 1942) reported approximately 106 cases from the United States and Canada. Of the patients 16 were born in the United States, most of them coming from eastern or southeastern Europe. At the International Congress of Otology, Rhinology and Laryngology held in Madrid, Spain, in 1932, an extensive survey was presented. Belinoff reported 2,351 cases up to that time. The disease occurs more frequently in women. It is most common in the nose and larynx. It is chronic and may be fatal, usually by obstruction.

Lichen Nitidus. Presented by DR. W. W. MURPHY and DR. B. HELD.

Fibrosarcoma of the Heel. Presented by DR. W. W. MURPHY and DR. B. HELD.

Fox-Fordyce Disease in a Girl Aged Twelve and One-Half Years. Presented by DR. BENJAMIN P. PERSKY.

Lupus Erythematosus with Chrysiasis. Presented by DR. DON R. PRINTZ for DR. H. N. COLE and DR. J. R. DRIVER.

swelling of the gums manifested that sign. He stated that tumors composed of monocytes are occasionally found. Haffly and Schipfer<sup>11</sup> reported such a case with bilateral nasal obstruction of twelve months' duration. The nares were found to be blocked by large, bluish gray irregular tumors, which bled easily on touch. Blue-gray nodules were present on the cheeks.

Montgomery and Watkins<sup>5</sup> in 1938 described 6 cases of exfoliative dermatitis due to monocytic leukemia. Lynch,<sup>11a</sup> Lamb and Stout<sup>11b</sup> and Montgomery and Watkins<sup>5</sup> described vesicular and bullous lesions due to monocytic leukemia. However, some of these were of the Naegeli type. We encountered no cases of exfoliative dermatitis due to monocytic leukemia in this series. Twenty-four of our 50 patients (48 per cent) had cutaneous manifestations. This compares well with Doan and Wiseman's<sup>7</sup> figure of 50 per cent. Twenty-five per cent had changes in the mucous membrane such as hypertrophy, hemorrhage or ulceration. Hemorrhages of the skin and mucous membrane tended to occur when the platelet count was low, although several patients had purpura with normal platelet counts. Large necrotic ulcers and gangrenous sloughs were present in the mouths of 3 patients, and others had large, fungating tumors of the soft palate. Similar findings have been reported in the literature by Loveman,<sup>9</sup> Evans,<sup>12</sup> Clough<sup>13</sup> and others.

The early infiltrated cutaneous lesions of monocytic leukemia may resemble secondary syphilis, according to Mercer<sup>14</sup> and Montgomery,<sup>5</sup> or mycosis fungoides (Montgomery<sup>5</sup> and Freeman and Koletsy<sup>15</sup>). Freeman also stated that coalescent nodules may form plaques which resemble Boeck's sarcoid.

Montgomery,<sup>5</sup> Freeman<sup>15</sup> and Osgood<sup>10</sup> found that specific lesions occurred in 10 per cent of the cases of monocytic leukemia, as compared with 8 per cent in lymphoid leukemia and 1 per cent in myeloid leukemia. In 16 per cent of our series there were definite infiltrated cutaneous lesions. These showed little scaling and ranged from 0.1 to 2 cm. in diameter. Macules, papules and nodules were often found on the same

11. Haffly, G. N., and Schipfer, L. A.: Subacute Monocytic Leukemia with Nasal Manifestations, *Arch. Otolaryng.* **31**:858-862 (May) 1940.

11a. Lynch, F. W.: Cutaneous Lesions Associated with Monocytic Leukemia and Reticulo-Endotheliosis, *Arch. Dermat. & Syph.* **34**:775-796 (Nov.) 1936.

11b. Lamb, J. H., and Stout, H. A.: Reticulo-Endotheliosis, *South. M. J.* **33**: 1117-1126 (Nov.) 1940.

12. Evans, T. S.: Monocytic Leukemia: General Review of Subject, *Medicine* **21**:421-456 (Dec.) 1942.

13. Clough, P. W.: Monocytic Leukemia, *Bull. Johns Hopkins Hosp.* **51**:148-177 (Sept.) 1932.

14. Mercer, S. T.: Dermatoses of Monocytic Leukemia, *Arch. Dermat. & Syph.* **31**:615-635 (May) 1935.

15. Freeman, H. E., and Koletsy, S.: Cutaneous Lesions in Monocytic Leukemia: Report of Two Cases with Pathologic Study, *Arch. Dermat. & Syph.* **40**:218-240 (Aug.) 1939.

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## ROLE OF THE CLINICIAN IN MODERN DERMATOLOGY

President's Address

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TONIGHT I have no scientific contribution, no announcement of a startling invention and no statistical study. We are living in an age when epoch-making discoveries crowd one another from the stage of life in rapid succession. Before we can fully evaluate the effect of one upheaval on the state of our established knowledge we must direct our thinking into another channel to adjust ourselves to something new again. Such continuous adaptation in the field of medicine, difficult though it is, may be accomplished by a mature and experienced mind. To a young physician who is still mastering the alphabet of medical thinking it must be so disturbing, however, as to make difficult the establishment of a permanent base. The great speed of our journey in the quest of knowledge makes it imperative that we stop looking forward occasionally, survey our present and direct our eyes backward to see where we have been. Let us make such a pause tonight.

The remarks I have to make will be addressed chiefly to the younger dermatologists and to the embryos in our midst. For my contemporaries and my elders I have only words of gratitude. In our specialty, probably more than in others, a man does not rise by his own efforts alone. He cannot by himself learn dermatology from books or from pictures or even from patients. He must be taught, he must be guided, and his errors must be corrected. To my colleagues I am indebted for opportunities given me for work and study, for their vast knowledge and experience which they have made available by the presentation and discussion of cases before this society and especially for their help in calling to my attention mistakes which I have made in patients who have left me. All too often we assume smugly that patients who do not return to us have been given correct diagnosis and treatment and are well. It is of great service to be informed when we are wrong. A mistake repeated a hundred times is not instructive, and it cannot be tabulated as experience. An error made once, however, and corrected promptly has educational value. It is a tribute to the genuine friendship and intellectual maturity that exist among the dermatologists of

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teriology or other laboratory fields, the apprentices, too, pursued training in those directions. But above all else they became good clinicians.

Today opportunities for such training are comparatively few. The number of physicians seeking to enter our specialty has increased tremendously, and it is impossible to provide an adequate preceptor for each potential apprentice. Furthermore, the laboratory aspects of dermatology have been developed so intensively and so far that few men are qualified by experience or facilities to teach them all. It has become necessary, therefore, to establish courses of instruction for larger groups in which students receive training in many branches of dermatology from teachers who are especially well qualified in those fields. Some of these teachers are practicing dermatologists; others, especially in the basic sciences, are strictly laboratory men. An attempt is always made to correlate all of the teaching, so that in the course of training students will dovetail all that they have learned into compact and well rounded-out patterns and will emerge fully prepared to stand on their own feet as practicing dermatologists. Are such concentrated departmentalized courses succeeding in this aim? In their contact with patients dermatologists stand or fall on their qualifications as good clinicians and on no other basis. Can any course of formal training by itself succeed in turning out dermatologists who are fully equipped for practice? It is unfortunate that in all formal teaching the emphasis is generally placed on the definite and dogmatic. It is much easier to help students to recognize, let us say, elastic fibers under the microscope, a culture of *Microsporon lanosum* or the blood picture in lymphatic leukemia than it is to transmit to them the composite of all impressions that we call clinical judgment. And yet this intangible clinical judgment must be possessed by every dermatologist before it is safe for him to establish his own office where he is alone with his patient and his conscience. Clinical judgment is not an inborn characteristic; it is always developed. It is the composite of keen observation, controlled experience and sound reasoning. In our time the powers of observation are being dulled by the plethora of gadgets at our command. We have the equipment and laboratory procedures to take our patients apart down to the very elements that compose them. We can analyze them physically and emotionally. We can even plot graphs to determine the course of their disease by barometric pressures.

It is a wholesome and a humbling experience to look back across the years to the men who did so much to advance the early knowledge of dermatology, who worked long before the advent of our many mechanical aids and who merely observed and reasoned. Among the interesting works of the old masters, there is nothing more fascinating than the writings of Ferdinand Hebra, whose treatise, "On Diseases of the Skin," was published between 1866 and 1880. It is remarkable

advantage. Repeated blood transfusions have little effect on the life expectancy but are of temporary value in elevating the red blood cell count, which is usually rather low, the anemia being of the macrocytic type in over 50 per cent of the cases.

The conditions in the following cases are illustrative of the cutaneous lesions seen in monocytic leukemia.

#### REPORT OF CASES

CASE 1.—In a white man aged 44 there developed a "boil" on the abdomen three months before admission to the Cleveland Clinic Foundation Hospital. In a short time similar lesions had appeared on the trunk and lower extremities. He had been weak and fatigued for two months. There was no favorable response to topical remedies and blood transfusions. On admission to the hospital he was pale and weak and obviously ill. He had three types of cutaneous lesions: (1) small,



Fig 1 (case 1)—Large ulcer on thigh simulating pyoderma gangrenosum. There was monocytic leukemia infiltration in margins of the ulcer.

infiltrated, light red papules and papulopustules on the trunk, many of which were follicular and showed central necrosis; (2) rounded deep ulcers with pink, indurated, precipitous and undermined margins on the thighs and legs (the ulcers varied from 4 to 10 cm. in diameter, and their bases were covered with a thick, foul, purulent exudate; the ulcers simulated those seen in pyoderma gangrenosum), and (3) a large dull red nodule on the lower portion of the abdomen. The central portion of the lesion was not so firm as the periphery and was considered an early cutaneous abscess.

The liver and spleen were not palpable, and superficial lymph nodes were not unusually enlarged. There were no lesions in the mouth.

Urinalysis showed normal findings. The hemogram showed a red blood cell count of 2,880,000, a hemoglobin content of 54 per cent, a volume index of 1.04 and a leukocyte count of 20,100, with 72 per cent neutrophils, 8 per cent lymphocytes, 1 per cent eosinophils and 19 per cent monocytes. An occasional monoblast was seen. Essentially the same changes in the blood were observed on repeated examinations. A sternal puncture showed hyperplastic bone marrow containing many monocytes. Wassermann and Kahn reactions of the blood were negative.

all the inflammatory changes in the skin can be produced by purely external causes. He thereby focused the attention of dermatologists on the skin as an organ of local as well as systemic disease. He did much to free the specialty of dermatology from the stifling dogma of constitutional dyscrasias which had so long obstructed progress toward rational diagnosis and treatment.

In general it may be said that diseases do not change; only our understanding of what is happening is subject to reinterpretation. It is a tribute to the care with which Hebra and other great clinicians of the past examined their patients, studied and classified their dermatoses and appraised the effect of treatment that even today we lean so heavily on the foundations of clinical dermatology which they built for us.

How can one develop clinical judgment? The basic ingredient is thorough examination of patients. An experienced clinician can often make a diagnosis after a fleeting glance. Into that glance, however, is poured the sum total of all his experience focused sharply on the interpretation of the problem at hand. The beginner has no such collection of clinical pictures in the file of his memory to draw on. For him each case is a new mystery the clues of which he must uncover one by one. He must school himself in the rigid discipline of some definite system for examining every patient. Only by searching for all possible evidence in each case can he guard himself against the risk of overlooking some one minute clue that may prove to be decisive. There is no basic training of greater value than the careful observation and description of morphologic data. It is the dermatologists' great fortune that the lesions which they examine are actually gross pathologic specimens so located on the surface that they can readily be examined during life. Let dermatologists then, like pathologists, examine minutely and describe thoroughly. Acquired early, the habit of such careful scrutiny makes a student's training more fruitful, for a person sees only what he recognizes. One case which is examined critically and understood is worth many in which the lesions are not interpreted correctly. The gross examination of the eruption often needs to be amplified by magnifying the pathologic changes through microscopic sections. In some diseases, as in tumors, such microscopic examination is essential to the diagnosis; in most, however, it merely offers additional clues for the differential diagnosis. At times one needs to draw on the aid of all possible laboratory procedures to elicit information that may aid in the diagnosis and treatment in a case. But at no time can the practice of dermatology become a laboratory science. All laboratory tests are fallible, and, again, the results of all laboratory procedures must be sagely evaluated. In all phases of his training the student should have the guidance of a dermatologist of experience so that all the facts which he masters may be valid and all his habits well grounded. For the

Staphylococcus albus, Escherichia coli and nonhemolytic streptococci had grown from the undermined margins of the ulcers.

Histologic examination of tissue obtained from intact papules and margins of the ulcer showed essentially similar changes. As would be expected, there was an acute inflammatory infiltration near the margin of the ulcer. This zone of reaction merged with areas of cellular infiltrate consisting chiefly of large, round, stellate and angular mononuclear cells. This type of infiltration involved most of the corium and extended into the subcutaneous tissue. The nuclei were large, oval, round or irregular and relatively pale. There was a fine nuclear membrane and chromatin network and large nucleoli. There was a moderate to abundant vacuolated cytoplasm. A few mitotic figures were present. Reticulum stain showed abundant reticulum in and next to the large angular cells. Small pyknotic, hyperchromatic nuclei were present.

The pathologists who studied the sections made a diagnosis of reticuloendotheliosis suggestive of leukemia. A final diagnosis of monocytic leukemia was made because of the persistent though moderate leukocytosis, the monocytic hyperplasia of the bone marrow and the abnormal differential blood cell counts. Some physicians might interpret this case as borderline between a well established case of monocytic leukemia and a case of aleukemia reticulosus, which has been discussed by Lynch<sup>11a</sup> and Wayson and Weidman.<sup>17</sup>

After a period of two weeks in the hospital this patient returned home, and he died two months later.

CASE 2.—A white woman aged 33 was admitted to Cleveland Clinic Foundation Hospital on Aug. 29, 1943. She had been well until June 17, 1943, when the initial symptoms of stiffness of the neck and sore throat developed. She had become acutely ill, with rapidly progressing weakness and continuous septic fever, and had received twelve blood transfusions. On admission the patient was weak and appeared to be acutely ill. Scattered over the trunk and extremities were numerous dull red to slightly violescent nodules with smooth, unbroken surfaces. Just below the right clavicle was a palm-sized infiltrated plaque. An ulcer with punched-out appearance was present in the region of the anterior pillar of the right tonsil. Tender lymph glands were palpable in the cervical regions, axillas and right inguinal region. The spleen and liver were not palpable.

The urine was normal except for a mild transitory albuminuria. Wassermann and Kahn reactions of the blood were negative. Heterophil agglutination was 1:128. The red blood cell count was 5,420,000; the hemoglobin content, 13 Gm. per hundred cubic centimeters, and the white blood cell count, 15,800 per cubic millimeter. Differential count showed neutrophils 47 per cent, lymphocytes 10 per cent and monocytes 43 per cent. Sternal puncture showed hypoplastic marrow with many monocytes and monoblasts.

Smears from the ulcer in the throat were negative for Vincent's organisms. Cultures showed Staphylococcus aureus and nonhemolytic streptococci.

During a period of six days in the hospital there was a continuous septic fever, the temperature ranging from 100.4 to 104 F., and a diagnosis of acute monocytic leukemia was made. Unfortunately, a biopsy specimen of a cutaneous lesion was not obtained. The nodules were identical with those observed in other cases of monocytic leukemia. The patient was discharged from the hospital unimproved.

17. Wayson, J. T., and Weidman, F. D.: Aleukemic Reticulosis: An Additional Member of Group of So-Called Cutaneous Lymphoblastomas, *Arch. Dermat. & Syph.* 34:755-774 (Nov.) 1936.

cyanide even when the tube was covered to intercept the ordinary light emanating from it. Within a few months this accidental discovery was translated into the practical application of using roentgen rays to diagnose fractures and to locate foreign bodies. The effect of roentgen rays on living tissues was also soon noted, and the first case of malignant disease which was successfully treated by roentgen rays, a rodent ulcer, was demonstrated by Stenbeck of Stockholm, Sweden, in 1899.<sup>2</sup>

Even more frequently advances have been made by observing and investigating customs that have been handed down through the ages. For centuries infusions of cinchona bark had been used successfully in the treatment of chills and fever. Eventually quinine was isolated from cinchona and was found to be a specific poison for the Plasmodium of malaria. Ephedrine is a comparatively recent addition to our armamentarium for the treatment of allergic diseases, and it too was isolated from a crude drug, ma huang, that had been widely used for centuries in China.

A good clinician permits himself to learn from his patients by observing with an unprejudiced mind the clinical experiments which they, at times unwittingly, perform. While still a boy, Jenner learned from neighboring farmers that an attack of cowpox prevented infection with smallpox. He performed his first inoculation with cowpox in 1796 and, after two years of successful experimentation, applied to the Royal Society for permission to present his observations before them. His request was rejected with the advice that he "ought not to risk his reputation by presenting to the learned body anything which appeared so much at variance with established knowledge and withal so incredible." It is the mission of the clinical investigator to work to free the established knowledge of his time as rapidly as possible from outworn prejudices and dogmas.

In all fields of medicine revolutionary changes in longheld concepts have occurred when clinicians have adjusted the pattern of their thinking to conform with the facts which were taught them by their patients. Since time immemorial patients with heart failure were put to bed in spite of the general experience of such patients that it was difficult to breathe while lying down. Their attacks of suffocation generally occurred in bed, and relief could be obtained only by their sitting up or walking around the room. Often patients with heart failure would be seen with edema of the legs and feet. Soon after, being put to bed such patients would lose the swelling of the lower extremities but would experience hydrothorax. The inferences from these simple observations were obvious: that fluid in the legs might be unsightly but that fluid in the lungs was suffocating and often fatal,

2. Cited by Pusey, W. A., and Caldwell, E. W.: *The Practical Application of the Röntgen Rays in Therapeutics and Diagnosis*, Philadelphia, W. B. Saunders & Co., 1903, p. 403.

CASE 3.—A white man aged 37 came to the clinic in February 1935, complaining of severe headache, failing vision, attacks of vomiting and ataxia. A clinical diagnosis of tumor of the brain was made. Craniotomy showed a medulloblastoma of the wall of the fourth ventricle. The hemogram showed a red blood cell count of 5,030,000 per cubic millimeter, hemoglobin content 94 per cent and white blood cell count 6,300. The differential count showed neutrophils 51 per cent, eosinophils 2 per cent, lymphocytes 37 per cent and monocytes 10 per cent. The Wassermann and Kahn reactions of the blood were negative. High voltage roentgen ray therapy was administered, and the patient was discharged, free of symptoms, on March 19, 1935.

He returned to the clinic on Nov. 6, 1937, complaining of palpitation of the heart when he climbed stairs. This symptom had been present for about a month. There were no other complaints. Two weeks later he complained of blurred vision and weakness. He became acutely ill and was admitted to the hospital on Dec. 16, 1937. On admission there were extreme pallor and weakness, numerous petechiae and ecchymoses on the trunk and extremities, hemorrhages from the gums and oral mucous membrane and gross hematuria. The spleen was palpable. On Nov. 27, 1937, the hemogram showed a red blood cell count of 1,040,000 per cubic millimeter, a hemoglobin content of 21 per cent (3.2 Gm.), a volume index of 1.23 and a color index of 95. The white blood cell count was 14,551 per cubic millimeter, with a differential count of 27 per cent neutrophils, 4 per cent lymphocytes and 69 per cent monoblasts.

On Jan. 12, 1938, following nine transfusions of 500 cc. of whole blood, the hemogram showed a red blood cell count of 2,160,000 and 5.5 Gm. of hemoglobin per hundred cubic centimeters of blood. The white blood cell count was 11,400, with a differential count of 28 per cent neutrophils, 2 per cent lymphocytes and 70 per cent monocytes. The platelets were reduced. Studies of bone marrow showed decided reduction of granulocytes and predominance of monocytes. The disease progressed rapidly, with increasing weakness, extensive purpura, repeated hemorrhages from the mucous membranes and a continuous septic fever, with the temperature ranging from 99.5 to 103 F. The patient died on Jan. 22, 1938. Post-mortem examination showed monocytic infiltration of the bladder, prostate, testicles, kidneys, liver and leptomeninges and also monocytic hyperplasia in the spleen, lymph nodes and bone marrow. There was a localized recurrence of the medulloblastoma. The mucocutaneous lesions were of the nonspecific type. Infiltrated papules and nodules were not observed.

CASE 4.—A man aged 46 was in good health until two months prior to his admission to the clinic on June 5, 1941. His chief complaints were weakness, enlarged glands, stiffness of the neck and an eruption of ten days' duration. Six weeks after the onset of his illness, his stools became tarry, he began to have hemorrhages of the mucous membrane of the mouth and petechiae developed on the legs, thighs and abdomen. The patient was admitted to the hospital for observation. Examination showed enlarged, tender cervical and postauricular lymph nodes. The spleen extended 2 cm. below the costal margin. The liver was not palpable. There were hypertrophy of the gums and petechiae on the hard palate. There were ecchymoses on the thighs and extensive purpura on legs, thighs and abdomen. While the patient was under observation, infiltrated, firm, pink papules and small plaques appeared on the chest. Sections of a firm papule showed a cellular infiltrate in the corium consisting of large mononuclear cells with large vesicular nuclei and prominent nucleoli. The cytoplasm was vacuolated. There were cells with indented or grooved nuclei, which were considered to be monocytes.

## ELECTROLYSIS VERSUS HIGH FREQUENCY CURRENTS IN THE TREATMENT OF HYPERTRICHOSIS

A Comparative Histologic and Clinical Study

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IN 1879 Michael<sup>1</sup> introduced the use of electrolysis for the permanent removal of hair, and since then it has been the method generally employed by dermatologists. According to Kovacs<sup>2</sup> the hair follicle is destroyed by electrolysis in the following manner: the sodium ions have positive charges and go to the negative pole (the needle) where they lose their charges and react on the water in the tissue to form sodium hydroxide (NaOH) and liberate hydrogen. The sodium hydroxide in turn destroys the cells adjacent to the needle. Hand<sup>3</sup> introduced a new type of apparatus equipped with a "switch" designed to decrease the shock and burning caused by rapid "make and break" of current. Marton<sup>4</sup> attempted to improve the rapidity of the operation by using multiple needles, but Cipollaro<sup>5</sup> disapproved of the use of more than one needle because of the difficulty of trying to insert properly into the follicles and to control at the same time eight to twelve needles. He suggested that the operator of multiple needles frequently inserted the needle into the skin but not into the follicle. Niemoeller,<sup>6</sup> who is not a physician, in 1938 published a book in which he reviewed the various methods of treating superfluous hair.

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Read at the Sixty-Sixth Annual Meeting of the American Dermatological Association, Inc., Hot Springs, Va., June 11, 1946.

1. Michael, C. E.: Trichiasis and Distichiasis: Reflections upon Their Nature and Pathology, with a Radical Method of Treatment, M. J. St. Louis Cour. Med. **1**:121, 1879.
2. Kovacs, R.: Minor Electrosurgery, M. Rec. **155**:163-165 (March 4) 1942.
3. Hand, E. A.: Electrolysis: Introduction of an Instrument for Relatively Painless Treatment, Arch. Dermat. & Syph. **45**:1094-1100 (June) 1942.
4. Marton, M. H.: Treatment of Hypertrichosis by Improved Apparatus and Technic, Arch. Phys. Therapy **21**:678-683 (Nov.) 1940.
5. Cipollaro, A. C.: Electrolysis: Discussion of Equipment, Method of Operation, Indications, Contraindications, and Warning Concerning Its Use, J. A. M. A. **111**:2488-2491 (Dec. 31) 1938.
6. Niemoeller, A. F.: Superfluous Hair and Its Removal, ed. 1, New York, Harvest House, 1939.



Fig. 2 (case 4).—Maculopapular and nodular eruption.



Fig. 3 (case 4).—Maculopapular and nodular eruption.

In 1942 Erdos-Brown<sup>16</sup> reviewed the literature on high frequency currents for the removal of hair and stated that vacuum tube diathermy is superior to the spark gap machine, because the former generates a sustained undamped current which flows smoothly in equal bursts of intermittent wave trains. She noted that an exposure of five hundredths to twenty hundredths of a second with a low current would destroy the papilla. She stated, "It is possible to perform epilation with the spark gap diathermy machine, but two electrodes are necessary, and one of these must be a directly applied and tightly bandaged metal applicator." With the vacuum tube current it is not necessary to use the directly applied metal secondary electrode. She observed that a few hairs returned after removal and stated, "Scar formation may be caused by too short a space of time between the treatments, too small interspaces between hairs or overdosage." She considered epilation with diathermy superior to epilation with electrolysis, as it caused less discomfort, was instantaneous, could not cause tattooage, and gave excellent cosmetic results and there was only occasional recurrence.

After employing electrolysis for ten years for the removal of superfluous hair, I was so impressed by the article by Erdos-Brown that I obtained a high frequency tube machine of the same make that she had used. Erdos-Brown<sup>16</sup> illustrated (on page 499) by a diagram the hook-up of the vacuum tube machine, which will not be repeated here. This machine is satisfactory for desiccating, coagulating and cutting operations. I used this machine over a period of eleven months for one hundred and twenty treatments. Four patients were given more than ten treatments and eight or nine treatments were administered to 4 others.

The power dial on the machine was not calibrated but had the words "increase power" in the center of the face of the dial. The power indicator was set at the letter "r" in the word "power" on the dial. In removing hairs with the monopolar short wave the current was turned on by tapping a foot switch. It was difficult to determine the exact time the current was on. The average rate was about two taps per second. It required twenty to thirty taps on the foot switch before a hair loosened. This consumed an average of ten to fifteen seconds. Then at least five seconds passed from the time that the needle was withdrawn and reinserted into another follicle and the current was again turned on. Therefore, approximately one hundred and twenty hairs could be removed in thirty minutes, if the operator worked rapidly.

The time consumed in removing hair with electrolysis varies greatly with the type of hair, the tolerance of the patient and the intensity of the current used. With  $1\frac{1}{4}$  milliamperes the average was twelve seconds

16. Erdos-Brown, M.: Superfluous Hair: Removal with the Monopolar Diathermy Needle. *Arch. Dermat. & Syph.* 46:496-501 (Oct.) 1942.

The hemogram showed a red blood cell count of 3,170,000; a hemoglobin content of 52 per cent, and a white blood cell count of 5,100, with a differential count of 2 per cent neutrophils, 20 per cent lymphocytes and 78 per cent monocytes. The platelet count was 110,000, coagulation time ten minutes and bleeding time four minutes. Clot retraction was normal. Sternal puncture showed an aplastic marrow with immature monocytes. High voltage roentgen therapy was administered, without improvement.

CASE 5.—A baby girl aged 3½ months was first seen on March 3, 1942. Shortly after birth several bluish areas had appeared over the trunk and extremities. Within three to four weeks the color of the lesions became less violescent but did not disappear completely. Within a month the lesions became more numerous and prominent.

There were numerous violescent cutaneous nodules scattered over the scalp, trunk and extremities and an area of infiltration involving the left external canal. The largest lesions were about 2 cm. in diameter. The spleen, liver and superficial lymph nodes were not palpable. Roentgenograms of the skull and chest showed normality.

The hemograms showed a red blood cell count of 3,400,000. Many nucleated red blood cells were present. The hemoglobin content was 61 per cent (9.5 Gm.) and the color index 90. The white blood cell count was 19,000, with a differential count of 16 per cent neutrophils, 37 per cent lymphocytes, 1 per cent eosinophils and 46 per cent monocytes. The platelet count was 260,000.

The disease progressed rapidly, and the child was taken to another hospital, where a diagnosis of monocytic leukemia was also made. Histologic examination of tissue removed from a nodule in the left scapular region showed no noteworthy changes in the epidermis and papillary layer of the corium. Throughout the corium there were areas of cellular infiltration almost obliterating the sebaceous and sweat glands. The infiltrate appeared to invade by separating the fibers of connective tissue. The cells were large and mononuclear, with poorly stained vesicular nuclei, a fine nuclear membrane and reticulated chromatin network. Large nucleoli were present in most of the cells. The cytoplasm was basophilic and vacuolated.

CASE 6.—A man aged 36 came to the clinic on Aug. 18, 1944, complaining of sore throat, swollen glands and an eruption. In July 1944, his throat had become sore. Within twenty-four hours lymph nodes on both sides of the neck had enlarged. Three weeks later "purple spots" had appeared on the trunk and arms. During the first month of illness he lost 24 pounds (10.9 Kg.), became progressively weaker and was troubled with vomiting. Symptoms were present for ten days prior to his entrance to the clinic.

Physical examination showed enlarged, discrete lymph nodes in the cervical, axillary and inguinal regions. The liver and spleen were enlarged and easily palpable. Tonsils were enlarged and firm. No infiltration was observed in the throat or mouth. There was a disseminated, macular, papular and nodular eruption involving the trunk and extremities. The eruption was most pronounced on the trunk and arms. The macules and papules were brownish red, while nodular lesions were bluish to violescent. The larger lesions seemed to involve the upper portion of the subcutaneous tissue. There were also old purpuric macules on the trunk and buttocks.

Wassermann and Kahn reactions of the blood were negative. A hemogram showed a red blood cell count of 5,140,000; a hemoglobin content of 87 per cent (13.5 Gm.) and a white cell count of 13,500, with a differential count of 29 per cent

administered in each area until the hair slipped out easily. On the examination of the serial section it could not be determined whether the minor changes seen were due to either method. The changes in the tissue were so slight that it was difficult to tell which follicles had been treated. The experiment was repeated, and the short wave was applied continuously for one to two seconds. Again the microscopic examination of serial sections was unproductive of information regarding damage to tissue.

ELECTROLYSIS (experiments on a living human subject).—An area on the chest of a white man aged 48 was anesthetized with 2 per cent procaine hydrochloride, and eight hairs of the terminal type were removed with electrolysis. The current

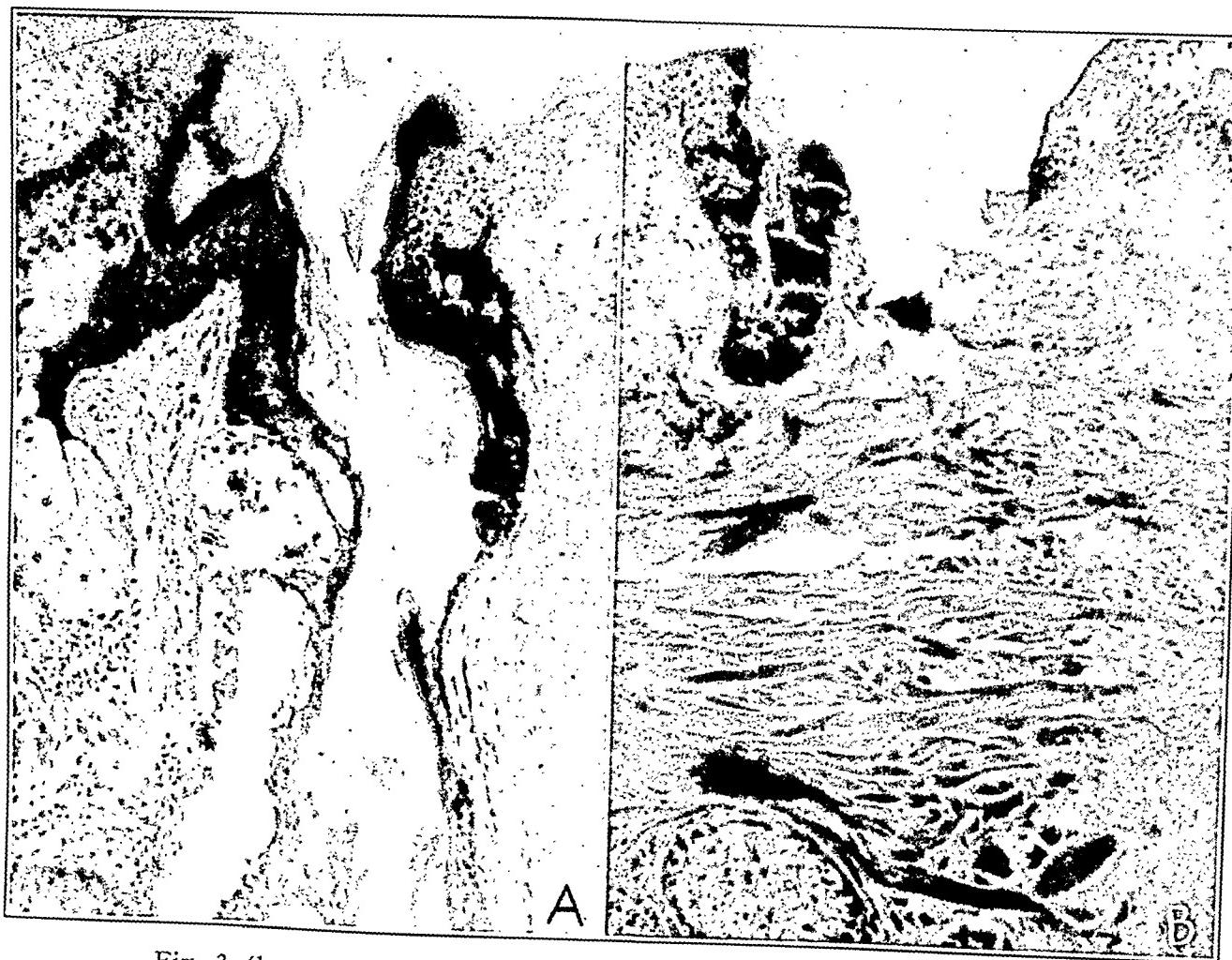


Fig. 3 (human tissue).—*A*, follicular changes due to treatment with vacuum tube high frequency current. In spite of the relatively strong current the destruction of the follicle is not complete. *B*, a nonfollicular lesion from the use of vacuum tube high frequency current. The changes in the epidermis are more destructive, but not as extensive as after electrolysis. Note that the zone of desiccation takes the form of a cylinder and not a cone.

was set at  $1\frac{1}{4}$  milliamperes, and the average time necessary for a hair to loosen was forty-five seconds. The needle was introduced into several nonfollicular areas, which were treated in a similar manner. A biopsy of each treated area was made immediately. The specimen, after fixation in a solution of formaldehyde, was cut into serial sections which were stained with hematoxylin and eosin.

neutrophils, 2 per cent eosinophils, 1 per cent basophils, 15 per cent lymphocytes, 15 per cent monocytes, 28 per cent monoblasts and 10 per cent fragile leukocytes. The volume of packed red cells was 102 per cent of normal, and the volume index was 0.99. Sternal puncture showed hypoplastic, immature marrow. A roentgenogram of the chest showed large hilar lymph nodes.

Histologic examination of tissue removed from a nodule showed a normal epidermis, except that it was thinned and its interpapillary portion was obliterated by the cellular infiltrate in the corium. There was edema of the papillary and subpapillary layers of the corium. Throughout the corium and extending into the subcutaneous tissue were areas of cellular infiltration, particularly around small vessels and about the pilosebaceous follicles. The infiltrate consisted chiefly of large mononuclear cells with vacuolated cytoplasm and large, round, oval and indented vesicular nuclei. The nuclear membranes were fine, and there was a



Fig. 4 (case 7).—Hypertrophy of the gums and a large area of necrosis on the palate.

delicate chromatin network. One or more large nucleoli were present. There were a few mitotic figures. Sections of an enlarged lymph node showed most of the normal structure of the gland replaced by cellular infiltrate identical with that seen in the skin. Reticulum stain showed a slight increase of reticulum in the involved areas.

The disease progressed rapidly, and the patient died at his home in March 1945.

CASE 7.—A woman aged 19 came to the clinic on Oct. 31, 1941, complaining of "sore mouth" of two months' duration. She had suffered from mild colitis for eight years. She had had five loose stools a day for four months prior to admission. She had gradually become weaker and had lost weight rapidly. The gums and mucous membrane of the palate had become thickened and sore during the past two months. There had been no oral hemorrhages. Changes in the oral mucous membrane were accompanied with pain and swelling of the left side of the face.

A summary of the comparative histologic changes which resulted from treatment with diathermy and electrolysis shows that the affected areas on the surface and the crater depressions in each case were similar, but may be smaller after diathermy. The rete cells of the follicle can be destroyed as completely with electrolysis as with high frequency currents, but with the latter agent the cells are replaced by a denser, more basophilic material and the changes seem to be more destructive and irreversible. The surrounding collagen was affected less with electrolysis than with short wave, and the changes were less basophilic and more granular. Experiments with tissue removed from a cadaver gave unsatisfactory results with either electrolysis or short wave.

#### INSULATED NEEDLES

It has been shown by histologic studies that after treatment with electrolysis or desiccation the greatest destruction of tissue occurs on or

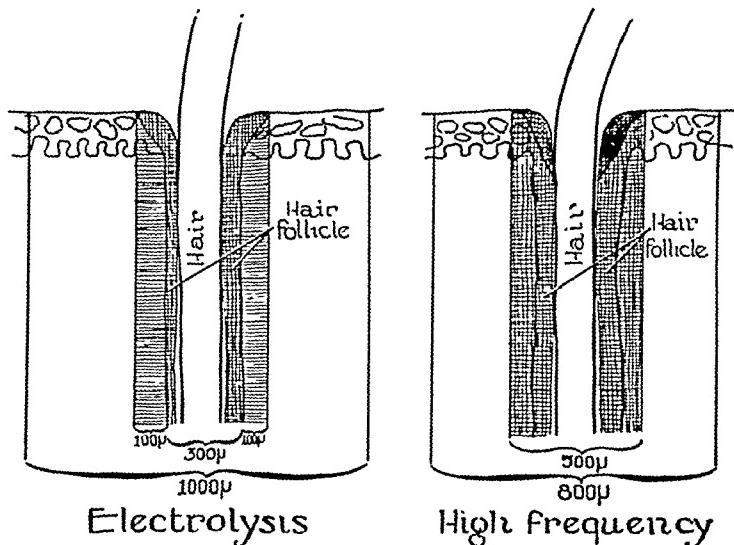


Fig. 4.—Schema showing the relative quantitative and qualitative destructive changes caused by the two types of currents in relation to the hair follicle.<sup>19</sup>

near the surface. There may be an advantage, therefore, in the use of insulated needles. Bordier<sup>7</sup> used a needle designed with an elliptic point and insulated in such a manner that only the tissue surrounding the papilla was desiccated. Bordier claimed that with his insulated needle the borders of the orifices of the follicles were not injured, while the hair papilla and the surrounding area were desiccated. Consequently, the destroyed follicles healed without visible scars.

An insulated needle must be introduced to the proper depth to be effective. The noninsulated part must pass beyond the papillary layer, but if it is inserted too deeply it will not burn the papillae of the hair follicles. The depth varies with the size of the follicles, and it is not

19. This illustration is from the Art Department of the University of Maryland School of Medicine.

There was diffuse hypertrophy of the upper and lower gums, and some of the teeth were almost covered with hyperplastic gum tissue. A large, firm, fungating mass with central necrosis involved most of the hard palate and a portion of the soft palate. The left side of the face was swollen and tender. The lymph glands in the cervical, axillary and the inguinal region were moderately enlarged. The spleen and liver were not palpable.

Wassermann and Kahn reactions of the blood were negative. The red blood cell count was 2,900,000 and the hemoglobin content 7.5 Gm. per hundred cubic centimeters. The white blood cell count was 26,150, with 14 per cent neutrophils, 8 per cent lymphocytes, 55 per cent monocytes and 23 per cent fragile leukocytes. The platelet count was normal, and the volume index was 103 per cent. Sternal puncture showed hyperplastic marrow consisting chiefly of monocytes. Six weeks later the white blood cell count was 48,500, with 40 per cent monocytes and 36 per cent fragile leukocytes.

The patient remained in the hospital for about six weeks, during which time there were frequent chills and a period of septic fever, with a temperature up to 104 F. The lesion on the palate developed into a large ulcer, and the disease continued to progress. The patient left the hospital in poor condition.

CASE 8.—A white man aged 55 came to the clinic on June 30, 1941, complaining of weakness and an eruption of three weeks' duration. In January 1941 he had had fifteen teeth extracted. Soon afterward he began to lose weight. He felt well but was unable to explain the loss in weight. Three weeks before he came to the clinic "red spots" had appeared on the face. Within a few days numerous lesions appeared on the face, trunk and extremities. There was no itching.

There were numerous, infiltrated, smooth, round flesh-colored to light red papules and small nodules scattered over the face, trunk, extremities and scalp. There were no petechiae or ulcers. The pharynx was abnormally red, but there were no intramucosal hemorrhages or hypertrophy of the gums. The liver, spleen and superficial lymph glands were not enlarged.

Urinalysis showed a heavy trace of albumin and many granular casts. Wassermann and Kahn reactions of the blood were negative. The red blood cell count was 4,490,000, hemoglobin content 81 per cent (12.5 Gm.), color index 10.90 and volume index 1.03. The white blood cell count was 16,200 with 7 per cent neutrophils, 8 per cent lymphocytes and 85 per cent monocytes, many of which were immature. The platelet count was reduced. Sternal puncture showed hypoplastic marrow composed chiefly of immature monocytes.

Examination of tissues removed from a nodule showed obliteration of the inter-papillary portion of the epidermis and the thinning of this layer by an extensive, loosely packed cellular infiltrate extending throughout the corium and into the subcutaneous tissue. The infiltrate consisted almost entirely of large mononuclear cells with little stroma. The cytoplasm was vacuolated, and the nuclei were vesicular, large, round, oval and indented. The nuclear membrane was fine, and there was a delicate chromatin network. One or more nucleoli were present. Some of the nuclei showed transverse folds. There were a few mitotic figures. The infiltrate was perivascular and abundant around the pilosebaceous follicles.

A diagnosis of monocytic leukemia was made, and the patient returned home. He later received low voltage fractional roentgen therapy. Shortly after this therapy was started the patient became acutely ill, and the disease progressed rapidly to a fatal termination.

discomfort usually decreased with subsequent treatments. Seldom was the pain so intolerable that the patient would discontinue treatments.

#### COMMENT

Electrolysis causes destruction of tissue by lysis due to local decomposition of tissue, which frees an alkali at the negative pole, the needle. High frequency currents generated by vacuum tube or spark gap machines cause destruction of tissue by the heat generated by the electric current concentrated at the needle electrode.<sup>2</sup> Electrolysis is slow, tedious and time consuming. Although there is a high percentage of recurrences when electrolysis is employed, it is considered to be more satisfactory than high frequency currents. Treatment with electrolysis rarely causes abscesses, and those that occur are always superficial and heal with imperceptible scarring. Deeper abscesses and depressed scars developed in several patients treated with short wave. It was my impression that most of the hair removed with high frequency currents apparently recurred unless the current was kept on long enough to cause visible burns, which healed with depressed scars. About ninety hairs from each breast of 1 patient were removed with diathermy at least three times over a period of three months, yet after several months all hairs had apparently recurred.

#### TECHNIC

A few points concerning the usual technic of treatment with electrolysis for hypertrichosis are listed. The patient grasps the moistened positive electrode. The needle (negative pole) is held by a needle holder which has a switch, and the current is turned on by the operator after the follicle is entered. A milliamperemeter is always used, and the current is adjusted to the tolerance of the patient ( $\frac{1}{2}$  milliampere to a maximum of  $1\frac{1}{2}$  milliamperes). Most operators agree that with either method the needle should be kept in the follicle with the current on until the hair slips out without any resistance, but when the hair loosens the entire follicle may not be destroyed.

It has not been accurately determined how much of the follicle can be left intact without the hair's regrowing. Also it is not known whether the hair follicle can regenerate only from the papilla and whether it can regenerate when a part of the wall is not destroyed. Therefore two recommendations for the treatment of persons with hypertrichosis are made to increase the efficiency of electrolysis. It is suggested that the current be continued for about ten seconds after the hair slips out without application of traction. When a hair regenerates it usually regrows with the same texture, color and shape as the original hair. Since hair follicles when partly regenerated may be more readily destroyed than when allowed to obtain their full growth,

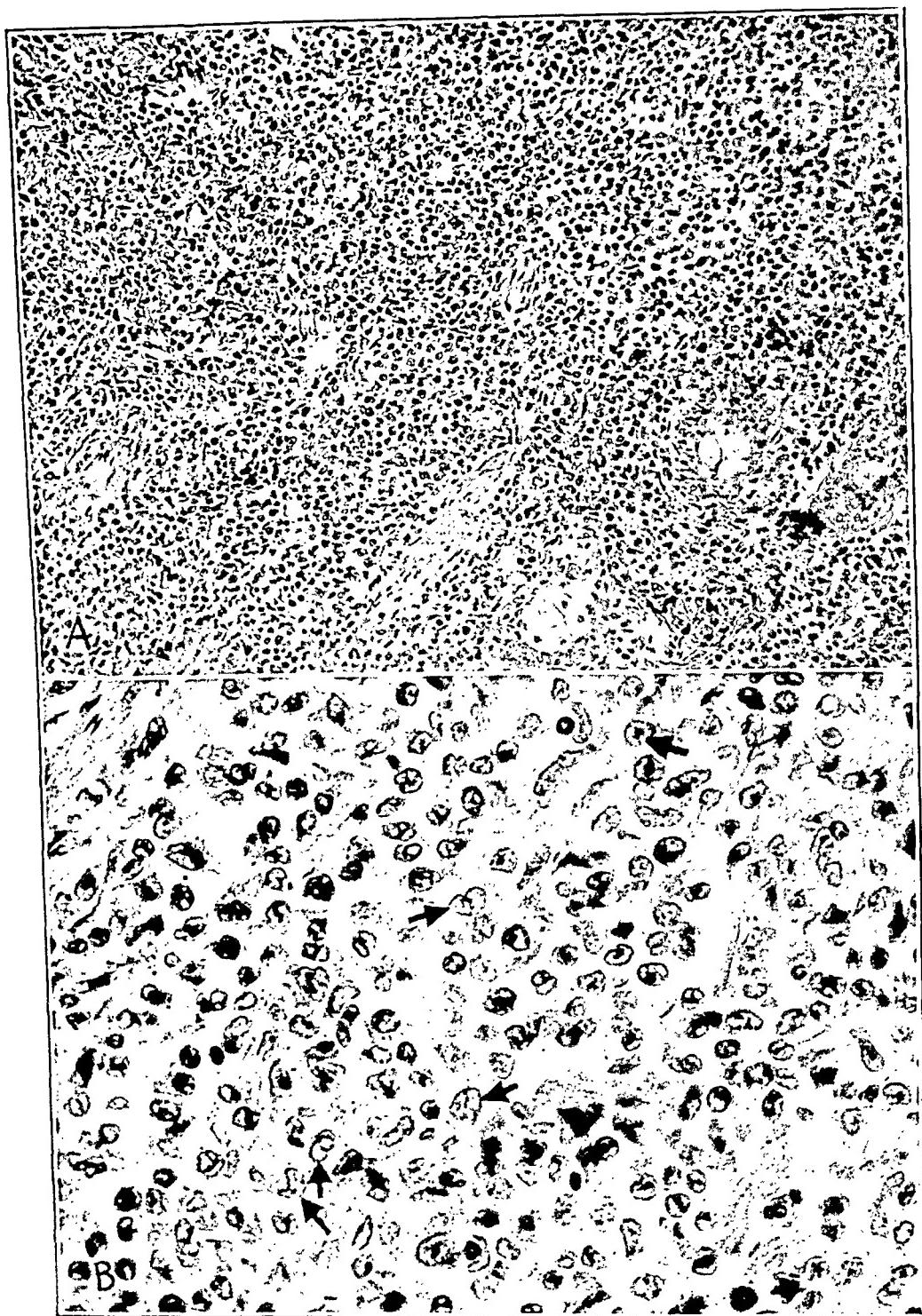


Fig. 5 (case 8).—A, diffuse mononuclear cellular infiltrate in corium.  $\times 150$ . B, numerous monocytes with sparse, delicate stroma. (Arrow points to monocytes.)  $\times 500$ .

Most women and young girls to whom I have given this treatment seem to be particularly immune to pain and peculiarly indifferent to minor scarring. Many times I have seen results with which I was entirely dissatisfied, but which satisfied the patients. However, I still think that we should use a process, such as Dr. Ellis has described, that gives the fewest recurrences, the best appearance without scars and the minimum amount of pain.

Dr. Ellis is to be congratulated on presenting a subject which we are likely to dismiss sometimes, because of our apparent familiarity with it, but which is important.

DR. PAUL E. BECHET, Elizabeth, N. J.: I also enjoyed Dr. Ellis' presentation. I have had the same results from treatment with high frequency current in patients with hypertrichosis as Dr. Ellis has had, and I have returned to the use of electrolysis. I do not know whether the untoward results which I observed occurred because of the rapidity of the action of the high frequency currents, but I am sure that results in my patients in relation to permanency, lessened pain and cosmetic effect were better in treatment with electrolysis than with high frequency current.

Dr. Ellis gives credit to Dr. Charles E. Michael, of St. Louis, for the discovery of the method. In this he is only partially correct. Michael used the method for the first time in 1875, but only for the destruction of "wild hairs" of the eyelids. It was William A. Hardaway who first introduced treatment with electrolysis in dermatology in 1877, but with his predilection for historical and biographic accuracy, as well as his innate fair-mindedness, he never wrote an article on electrolysis without giving due credit to Charles E. Michael.

DR. ANTHONY C. CIPOLLARO, New York: Dr. Ellis deserves to be congratulated on doing detailed and intricate research. He was kind enough to send me a copy of his paper before the meeting, which I read and studied carefully, and I prepared a discussion, but before reading my notes I should like to discuss three things which he emphasized.

First, regarding the apparatus he used, most of the work was done by the tube machine, and we have observed that tube high frequency machines are not so suitable for this type of work as spark gap machines, which produce a damped current. Perhaps these are, in part, the reasons that his treatments have not been particularly effectual.

I agree with Dr. Ellis in his statement that high frequency currents produce a cylindric type of destruction. Dr. MacKee and I published photographs in "The Principles and Practice of Physical Therapy" in 1932 showing that type of destruction, and, with your permission, I should like to show you a slide to illustrate this.

Dr. Ellis has emphasized the fact that the coagulating current is too destructive in epilation. Destruction of tissue with high frequency currents is dependent on two factors: the strength of the current and the duration of the application. It is a multiple of the time and the amount of current, so that if one uses a little time and a lot of current one will get a great deal of destruction, or, also, if one uses a little current and a lot of time one will get a great deal of destruction.

In the main I agree with everything that Dr. Ellis has said. There are a few points on which I should like to elaborate. Dr. Ellis has quoted me as disapproving the use of more than one needle in treating patients with hypertrichosis with the galvanic current. I oppose the multiple needle technic because, first, it is difficult to hold in place and control more than one needle

## COMMENT

Although the first case of monocytic leukemia was reported by Reschad and Schilling-Torgau<sup>1</sup> and Naegeli,<sup>2</sup> whose views on the origin of the monocyte were published in 1923, it was not until after the excellent article on monocytic leukemia by Clough<sup>13</sup> that there was a real interest in this type of leukemia. During the past fifteen years the literature on monocytic leukemia has grown rapidly. Leukemic reticuloendotheliosis is synonymous with monocytic leukemia. Articles have appeared with reference to the relationship of aleukemic reticuloendothelial hyperplasia to monocytic leukemia and the importance of reticulosclerosis as it pertains to a better understanding of the complex problem of lymphoblastomas. Wayson and Weidman<sup>17</sup> reported a case of aleukemic reticulosclerosis which simulated the clinical picture of granuloma fungoides and other lymphoblastomas. They stressed the importance of studies of the blood and the examination of bone marrow from the sternum in cases of lymphoblastoma. Lynch,<sup>11a</sup> Lamb and Stout,<sup>11b</sup> Foord<sup>18</sup> and Feller and Risak<sup>19</sup> considered aleukemic reticuloendotheliosis to be aleukemic monocytic leukemia. As far as we have been able to determine, this view remains to be proved. In this series of cases the initial hemogram sometimes failed to show a leukocytosis, and at times there was a leukopenia. However, the high monocyte count in the blood smears and studies of bone marrow confirmed the diagnosis of monocytic leukemia. Subsequent studies of the blood always showed a leukocytosis as well as smears of the blood characteristic of monocytic leukemia.

The so-called Naegeli type of monocytic leukemia has been observed at Cleveland Clinic Foundation Hospital. However, exfoliative dermatitis and other cutaneous lesions described by Montgomery and Watkins have not been observed in this type of leukemia. After a review of the literature and after consideration of the recorded deliberated opinion of hematologists regarding the derivative of the monocyte, it seems proper to consider the Naegeli type of monocytic leukemia as a variant of myelogenous leukemia.

We have not determined the incidence of monocytic leukemia seen among the cases of leukemia observed at the clinic. Doan and Wiseman<sup>7</sup> found 16 per cent of monocytic leukemia in a series of 76 cases of leukemia. Fifty per cent of their patients had cutaneous lesions. Montgomery,<sup>5</sup> Freeman<sup>15</sup> and Osgood<sup>10</sup> reported the incidence of specific cutaneous lesions in the leukemias to be 10 per cent in monocytic, 8 per cent in lymphatic and 1 per cent in the myeloid type.

18. Foord, A. G.; Parsons, L., and Butt, E. M.: Leukemia Reticulo-Endotheliosis (Monocytic Leukemia), with Report of Cases, *J. A. M. A.* **101**:1859-1866 (Dec. 9) 1933.

19. Feller, A., and Risak, E.: Zur Kenntnis der Reticuloendotheliosen, *Folia haemat.* **43**:377-392 (Feb.) 1931.

and that every dermatologist throughout the country should make all possible efforts to prevent the mushrooming of these establishments.

Another disconcerting incident has recently occurred. In November 1945, the patent office issued a patent for a so-called "x-ray razor." I examined the patent thoroughly, and it is nothing more than a roentgen-ray machine. The roentgen rays are filtered through a column of water enclosed within two layers of aluminum.

I congratulate Dr. Ellis on his presentation and thank him for giving me the opportunity for discussing this paper.

DR. DONALD M. PILLSBURY, Philadelphia: The matter of the permanent removal of hair and the study of Dr. Ellis have an importance which I think may not be generally appreciated, and that is in connection with war wounds. Many soldiers and sailors who have had to undergo extensive plastic procedures because of wounds may have skin grafts which come from areas which are hairier than the areas to which they are grafted, or there may occur, particularly on the face and sometimes on the scalp, unsightly tufts, or islands, of hair in the midst of scar tissue. The subject has been considered of such importance that there is a rather extensive study being done of the whole matter by the Surgical Division of the Surgeon General's Office. This study by Dr. Ellis, I think, is important from that standpoint.

DR. FRED D. WEIDMAN, Philadelphia: May I ask Dr. Ellis whether his sections showed any effects on the sebaceous glands in his subjects? The emphasis, naturally, is on the hair follicles, but I am curious to learn whether there was an effect also on the sebaceous glands. There is certain destruction of the epithelium of the common excretory ducts of the follicle and the sebaceous glands. I suppose that the answer is in the end result, namely, that (retention) sebaceous cysts do not follow this procedure, and I suppose that that implies regeneration of the epithelium in such a perfect way that it accommodates the secretion of the sebaceous glands.

DR. FRANCIS R. ELLIS, Baltimore: I wish to thank the discussers. Dr. Bechet is correct about Dr. Hardaway, and I think that most textbooks give him the credit.

As to the question raised by Dr. Weidman regarding the sebaceous glands, there is a liquefaction of the fats in the sebaceous glands near the needle, but the periphery of the glands is not affected. To prove what happens to the ducts, one may have to make a wax model from serial sections, as it is difficult to follow the ducts in the sections.

I have seen several patients with conditions similar to those mentioned by Dr. Pillsbury. The patients had skin grafts taken from a hairy region. One was a boy who had a burn across his forehead. The graft was made when he was a child, and when he became an adult a heavy growth of hair appeared in the graft.

I tried the Peerless machine a few times and made histologic sections from a specimen from 1 patient. The total amount of current depends on the time plus the intensity. I started with the settings at 30 and increased to 40 and finally to 50 on the two terminals, but histologic studies showed no changes in the hair follicles. The human experiment was a failure, due apparently to an error in technic. An experiment on a rat showed changes similar to changes which occur with the use of short wave.

I have repeated the human experiments with the Bovie apparatus, and I expect to continue these studies.

In this series cutaneous lesions were observed in 24 patients, or 48 per cent of the cases. The incidence of specific lesions was 16 per cent. Nonspecific lesions were commoner and occurred separately or in conjunction with specific lesions. Purpura and ecchymosis were the commonest types, with an incidence of 30 per cent. Pruritus was a troublesome symptom in only 2 cases, and intensely pruritic papular leukemids which occur in lymphatic leukemia were not observed. Likewise, there were no vesicular or bullous eruptions. Four per cent of the patients were jaundiced, and furunculosis occurred in 6 per cent of the cases. In 1 patient there developed ulcers simulating pyoderma gangrenosum (case 1). Hypertrophy of the gums, hemorrhages of the oral mucosa and ulcerations in the mouth and throat were seen in 50 per cent of the cases. These findings are in close agreement with those of Forkner,<sup>20</sup> Osgood<sup>10</sup> and Doan and Wiseman.<sup>7</sup> Forkner stated that the diffuse hypertrophy of the gums, usually with ulceration and necrosis, is characteristic of acute monocytic leukemia and expressed the opinion that these findings justify a tentative diagnosis of acute monocytic leukemia independent of the studies of the blood.

The specific eruption was usually polymorphous in type, consisting of light red or brownish macules and red to violescent nodules. The frequent occurrence of violescent nodules as specific cutaneous lesions of monocytic leukemia has been mentioned by several authors who have emphasized this type of lesion as an important clinical feature of monocytic leukemia cutis. The nodules are sometimes tender, but ordinarily the eruption is asymptomatic.

Monocytic leukemia is frequently an acute disease. This was demonstrated in our series of cases. However, chronic monocytic leukemia does occur. Doan and Wiseman<sup>7</sup> stated that there is no clinical syndrome which is pathognomonic of monocytic leukemia. It may be chronic or acute and occur at any age. There may be aleukemic or leukemic conditions of the blood.

The symptoms in our cases corresponded closely to those in cases reported in the literature. General malaise, septic fever, weakness, loss of weight, mucocutaneous hemorrhages and hypertrophy of the gums were the most prominent and frequent features. Weakness and fever were the chief complaints of 52 per cent of out patients, while 12 per cent came to the clinic because of an eruption. There was no particular sex incidence, and the age of the patients ranged from 3½ months to 78 years. The disease progressed rapidly in most of our cases, terminating in death on the average of eight and four-tenths months after the onset of illness.

20. Forkner, C. E.: Clinical and Pathological Differentiation of Acute Leukemias, with Special Reference to Acute Monocytic Leukemia, *Arch. Int. Med.* 53:1-34 (Jan.) 1934.

the characteristic brownish, hard papules were present in large numbers on the neck, arms, forearm, legs (particularly below the knees) and lower part of the trunk. The scalp resembled rather severe seborrhea. Flat, wartlike lesions were present on the backs of the hands, and minute follicular depressions were present on the palms. Her intelligence is low; she is an inmate of an institution for the mentally defective. She is a sister of the patient in case 4, and her father was found to be suffering from Darier's disease also, which he had first noticed in his seventy-fifth year. The familial relationship of these 3 patients is shown in figure 1, those affected being marked as black disks.

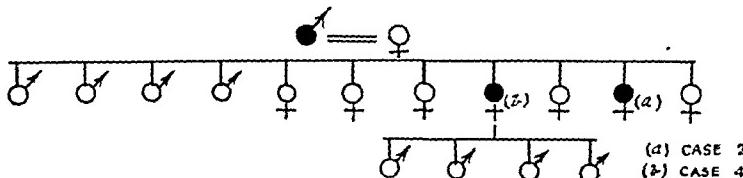


Fig. 1 (case 2).—Familial relationships of the patient in case 3. The affected patients are indicated by the black disks.

Unfortunately, her mental condition made dark adaptation tests valueless, and war conditions prevented estimation of the plasma vitamin A content, so that we do not know the state of her vitamin A nutrition before treatment was begun. A dark adaptation test on a normal sister gave a normal result. The wartlike lesions on the backs of the hands were not altered by treatment with vitamin A, though considerable improvement occurred elsewhere.

**CASE 3.**—Miss R., aged 9, had severe Darier's dyskeratosis. Pigmented papules were most distinct on the neck and calves, though present in large numbers on the forearms and elsewhere. Her intelligence was somewhat below normal. She

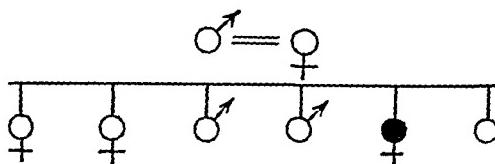


Fig. 2 (case 3).—Immediate familial relationship of Miss R. The patient is indicated by the black disk.

had been given small doses of vitamin A before we saw her. Her health is excellent, and no other member of the family has been affected by trouble with the skin. Her immediate relations are shown in figure 2.

**CASE 4.**—Mrs. P., aged 42, a sister of the patient in case 2, had well marked Darier's dyskeratosis, lesions being most plentiful on the scalp, neck and trunk and present to a lesser degree on the limbs. Her mental condition is subnormal, making her unsuitable for dark adaptation tests and altogether uncooperative. None of her four sons showed any sign of trouble with the skin. Her skin was better during pregnancy and always worse during summer.

**CASE 5.**—Mrs. W., aged 34, had typical Darier's disease, with characteristic pigmented papular lesions on the neck, trunk and limbs, most clearly marked below the knees. This patient said that her skin also became better during pregnancy, but, in contradistinction to the disease in case 4, it improved in summer and after exposure to sunlight. Her general health is good. None of her children or other members of her family have any trouble with their skin.

In monocytic leukemia, as in other types of the disease, the spleen, liver and lymph glands may be enlarged. In this series the spleen was palpable in 24 per cent, the liver in 20 per cent and the lymph glands in 24 per cent of the cases. Monocytic leukemia infiltrate was present in various viscera in case 3 and in a lymph node removed in case 4.

The histopathologic changes in specific lesions of monocytic leukemia have been ably described by Loveman,<sup>9</sup> Montgomery<sup>5</sup> and his associates, Lamb and Stout,<sup>11b</sup> and others. Our findings were in accord with those recorded in the literature. Biopsies were made in selected cases, some being recorded in the cases herein reported. The histopathologic findings were essentially the same in all specimens. The epidermis is thinned by the pressure of the cellular infiltrate, which involves most of the corium and frequently extends into the subcutaneous tissue. The infiltrate consisted of a few lymphocytes, fibroblasts, a variable amount of reticuloendothelial hyperplasia and abundant large mononuclear cells. Multinucleated or giant cells were not observed. There were a few mitotic figures. The predominant large mononuclear cells were loosely packed and perivascular and occurred in large numbers about the pilosebaceous follicles within and surrounding the sweat glands. There was a variable amount of vacuolated basophilic cytoplasm. The nuclei were large, round, oval, irregular or dented. Some nuclei were kidney shaped, while others were traversed by distinct bands of chromatin, giving the nucleus a grooved or folded appearance (fig. 6). According to Montgomery and Watkins<sup>21</sup> these cells are tissue monocytes. The nuclei are vesicular, not deeply stained, have a fine but distinct membrane and contain a network of chromatin. Each nucleus usually contains one or more large nucleoli. The interstitial fibers are delicate or sparse. In some cases fixed tissue cells were a conspicuous feature of the histologic picture; however, the large mononuclear cells of the monocytic type were present in small groups or scattered throughout the cellular infiltrate.

There is no treatment which is helpful in monocytic leukemia. Roentgen therapy is of little value in prolonging life, and occasionally it hastens the progress of the disease. Iodides and a solution of potassium arsenide at times give some relief of symptoms. The disease is invariably fatal.

#### SUMMARY

1. Fifty cases of the Schilling type of monocytic leukemia have been reviewed. The symptomatology, clinical features and hematology have been discussed briefly, and special emphasis has been given to the incidence and types of mucocutaneous lesions seen in this type of leukemia.

21. Montgomery, H., and Watkins, C. H.: Monocytic Leukemia, Cutaneous Manifestations of Naegeli and Schilling Types: Hemocytologic Differentiation, Arch. Int. Med. 60:51-63 (July) 1937.

*Results of Vitamin A Therapy in Seven Cases of Darier's Disease*

Case	Age, Yr.	Sex	Before Vitamin A Therapy				After Vitamin A Therapy			
			Plasma Vitamin A, Inter- national Units/ 100 Cc.	Caro- tene, Mg./ 100 Cc.	Result of Dark Adaptation Test*	Total Vitamin A, International Units	Duration of Treatment, Mo.	Plasma Vitamin A, Inter- national Units/ 100 Cc.	Caro- tene, Mg./ 100 Cc.	Dark Adaptation Test, Average Improvement Over Range Tested
1	33	M	Since childhood	..	..	Subnormal	3,000,000	3	..	0.1 log unit
2	30	F	Lifelong	..	..	Subnormal	25,000,000	30	112	44
3	9	F	6 yr.	..	..	Subnormal	30,000,000	10	308	69
4	42	F	Many years	69	87	Subnormal	900,000	1	..	.....
5	31	F	3 yr.	134	81	Slightly subnormal	9,200,000	3	124	90
6	19	F	1 yr.	52	..	Slightly subnormal	21,000,000	7	106	46 (<0.05 log unit)
7	13	F	8 yr.	87	85	Slightly subnormal	12,000,000	4	122	75 0.2 log unit

\* Dark adaptation test and normal values as described by Yudkin (1941) using a Crookes D.A.T. Range of brightness values of test object used were from 6.0 millimicros 1 log units to limit threshold values (average approximately 3.5 millimicros 1 log unit).

2. Monocytic leukemia may be chronic but is oftener an acute disease with severe constitutional symptoms, and it progresses rapidly to fatal termination.

3. There is a much higher incidence of mucocutaneous lesions in monocytic than in lymphatic or myelogenous leukemia. In approximately 50 per cent of the patients with monocytic leukemia there develop mucocutaneous lesions of either the specific or the nonspecific type or both.

4. Hypertrophy of the gums accompanied with areas of necrosis and ulceration of the oral mucosa, cutaneous hemorrhages and hemorrhages of the mucous membrane are common features of monocytic leukemia but cannot be considered as pathognomonic of the disease.

5. In monocytic leukemia the hemogram may show leukopenia or relatively moderate leukocytosis as compared with that observed in lymphatic and myelogenous types. The diagnosis is ultimately determined by the characteristics of the blood smear and the bone marrow obtained by sternal puncture.

6. Histopathologic changes in specific lesions of monocytic leukemia cutis are usually characteristic, but it is not uncommon for a general pathologist to return a diagnosis of sarcoma.

#### ABSTRACT OF DISCUSSION

DR. HARRY L. ARNOLD, Honolulu, Hawaii: I have neither seen nor had the opportunity to review the findings on anything like 50 cases. I once saw 1 case.

There are certain features of the disease which Dr. Hubler did not have time to discuss. Terminology, I think, is worth mentioning. The literature continues to contain the terms Schilling type and Naegeli type of monocytic leukemia. It seems to me that the time is ripe or past due to abandon these confusing terms, which have no particular meaning any more, now that the nature and the method of diagnosis of the disease have become established. There is just one monocytic leukemia, just as there is one lymphatic leukemia, which may be leukemic or aleukemic. There is no particular type of the disease. The "Naegeli type" is now known to be myelogenous leukemia mimicking the monocytic form of the disease. I think that the persistence of these terms just creates confusion and serves no useful purpose at all. The other term which still appears in the literature is the term "reticulos and aleukemic reticulos" or "leukemic reticulos." It is extremely confusing. I think that it would be well to abandon that too. It was useful during the early years of study of this disease, when it was by no means certain that one was dealing with a leukemia, either aleukemic or leukemic. It served the purpose of permitting a man to discuss the disease without committing himself on that score. I think that it is time the dermatologists committed themselves and did not use that term.

As to the diagnosis of the disease, Dr. Hubler's chief point was well taken. An alert hematologist is the important thing. The disease may be suspected on clinical grounds by physicians who have had the good fortune to see cases of it or on the basis of the pictures that Dr. Hubler showed. Interestingly, some of these pictures, particularly the divisions in the last one, were virtually identical, as might be

however, that the observations on the dark adaptation tests could not be correlated with the clinical picture in all cases.

The conditions, then, required to show that Darier's dyskeratosis is caused solely by deficiency of vitamin A are not fulfilled, and it becomes necessary to find another hypothesis. The one which seems to us to fit the facts most satisfactorily is that the epithelial cells of the skin are unable to make use of the vitamin A available in a normal manner. This idea is consistent with the common finding of normal amounts of vitamin A in the plasma, as mentioned previously. It may also possibly explain why in cases in which both estimation of plasma levels and dark adaptation tests were carried out before vitamin A was given the curves were subnormal in each case though the plasma vitamin A level was normal. Such results suggest either that the synthesis of vitamin A-containing substances (e. g., photochemical pigments) is defective or that there is some interference with the normal use of such substances by the tissues concerned (Wise and Sulzberger, 1941, and Sulzberger and Baer, 1943<sup>24</sup>).

Attempts to explain the pathogenesis of Darier's disease on a histologic basis have been made by Brunauer (1925)<sup>25</sup> and Goodman and Pels (1939, 1941).<sup>26</sup> It has been shown by these authors that the fundamental changes in Darier's dyskeratosis are multiplication of the basal cells with downward prolongations and absence of prickles. The cells do not adhere one to another in the usual way; lymph collects between them, and lacunas and fissures appear. Keratinization does not take place in a normal manner; instead, affected cells undergo degenerative changes and form either "grains" or *corps ronds*. Not only is the primary function of keratinization grossly disturbed, but another function of the basal cells—the formation of pigment—is also seriously affected (Mu, 1930).<sup>25</sup> Thus the development of these cells is so disorganized that two of their most important functions, keratinization and pigment formation, do not take place in a normal manner. It is suggested that another function of the basal cells is more or less upset in Darier's disease, that is, the ability to utilize vitamin A or its derivatives in a normal manner or to synthesize vitamin A-containing compounds as required. It is

24. (a) Wise, F., and Sulzberger, M. B.: The 1941 Year Book of Dermatology and Syphilology, Chicago, The Year Book Publishers, Inc., 1942, p. 450.  
(b) Sulzberger, M. B., and Baer, R. L.: The 1943 Year Book of Dermatology and Syphilology, ibid., 1944, p. 199.

25. Brunauer, S. R., in Jadassohn, J.: Handbuch der Haut- und Geschlechtskrankheiten, Berlin, Julius Springer, 1931, vol. 8, pt. 2, p. 210.

26. (a) Goodman, M. H., and Pels, I. R.: Bullous Dyskeratosis of the Keratosis Follicularis (Darier) Type, Arch. Dermat. & Syph. 44:359 (Sept.) 1941.  
(b) Pels, I. R., and Goodman, M. H.: Criteria for the Histologic Diagnosis of Keratosis Follicularis (Darier): Report of a Case with Vesiculation, ibid. 39:438 (March) 1939.

expected with lepromatous leprosy. This would be expected, of course, because both lepromatous leprosy and cutaneous lesions of this disease consist merely of huge aggregations of histiocytes, in this case monocytes and in the case of leprosy less fully differentiated histiocytes.

The involvement of the skin in this disease occurs with greater frequency than is the case with lymphatic or myelogenous leukemia, as might be expected, because this is a neoplasm of the reticuloendothelial system and the skin is distinctly a reticuloendothelial structure in the sense that it is not primarily a lymphatic structure or a myelogenous one. It is natural, therefore, that when neoplasia occurs in the reticuloendothelial system the skin ought to be more frequently involved than in the case of leukemias in which it is involved by other types of cells.

DR. LOUIS H. WINER, Beverly Hills, Calif.: The point that interests me in the diagnosis of monocytic leukemia is that, as the essayists said, a competent hematologist must be had in consultation. One can diagnose leukemia from tissue, but the type is more difficult to recognize because the cells of the circulation can be stained and studied in greater detail than those fixed in preservatives such as solution of formaldehyde or alcohol and then stained with hematoxylin and eosin. An imprint taken from fresh tissue and stained with Wright's stain is much more diagnostic than a section whose cells are shrunk by fixation. Because of this shrinkage the type of leukemia is frequently missed in the study of a section of a fixed tissue. It is unlikely that one can determine the type of leukemia after a patient's death from pathologic sections alone.

In 22 cases of monocytic leukemia collected at the Los Angeles County General Hospital in the past five years, that is, from 1940 to 1945, 12 patients were males and 10 were females. The youngest patient was 3 years old, and the oldest was 68. Seventeen of these 22 patients had changes in the gums, swelling, ulceration and bleeding; 16 had generalized enlargement of the lymph nodes, and 8 had purpuric hemorrhages in the skin. One patient had an ulcer similar to the type shown here this morning, and another patient had nodular plaquelike infiltrations. The authors are fortunate to have seen such interesting clinical manifestations on the skin. From our records, my colleagues and I agree with Montgomery in that about 10 per cent of our patients had cutaneous lesions other than purpura. The essayists also brought in the question of mycosis fungoides. I think that as time goes on and more knowledge about monocytic leukemia is acquired it probably will be possible to put mycosis fungoides in a category of the aleukemic form of monocytic leukemia. Dr. Montgomery and Dr. Watson in their paper showed that the terminal phase in some of their cases of mycosis fungoides was frank monocytic leukemia.

DR. FRANCIS P. McCARTHY, Boston: I recently reported a case of monocytic leukemia in which the lesions were primarily noted in the oral cavity. The development of these lesions was such that, as the process went on, gangrenous stomatitis developed that was so well shown among the slides here today. As I understand monocytic leukemia, it represents about 3 per cent of the leukemias that are met in routine cases in hospitals. In a recent survey of a three hundred bed hospital over a period of ten years, my colleagues and I had about 50 cases of leukemias of various types, with a single case of monocytic leukemia. The diagnosis of this disease can be made relatively early by biopsy of a specimen of the gingival tissue. The gum tissue is extremely susceptible in the dentulous mouth, and there is a further secondary infection from the organisms normally found about the necks of the teeth. The Vincent organisms definitely become active in this disease, and there is distinct sloughing, especially on the under surface of the intradental papillae. The patient suffers greatly from the oral lesions, and anything that one

## TREATMENT OF CUTANEOUS TUBERCULOSIS WITH LARGE DOSES OF VITAMIN D<sub>2</sub>

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MINNEAPOLIS

AND

RICHARD J. STEVES, M.D.

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DURING the last two years numerous reports have appeared in the European literature concerning the use of vitamin D in the treatment of cutaneous tuberculosis. Investigators in Belgium, France and England independently investigated the oral administration of large doses of vitamin D<sub>2</sub>.

In the years which followed the announcement by Steenbock and his colleagues<sup>1</sup> of an antirachitic substance in irradiated sterols, Malmström, Villaret, Justin-Besançon and Fauvert, Bergmann<sup>2</sup> and others discovered that these new forms of vitamin D were useful in the treatment of various types of tuberculosis.

In 1930 Levaditi and Po and Spies<sup>3</sup> reported that experimental tuberculosis in rabbits was distinctly benefited by the administration of large doses of irradiated ergosterol. These investigators observed that tuberculous tissue had a selective tendency to become calcified under the influence of this substance. A mineral shell formed around the areas of necrosis, and within this shell the tubercle bacilli were observed to be

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From the Division of Dermatology of the University of Minnesota, Dr. Henry E. Michelson, Director.

1. Steenbock, H.; Nelson, M. T., and Black, A.: Determinations of Vitamin A, *J. Biol. Chem.* **59**:ix (Feb.) 1924. Steenbock, H., and Black, A.: Fat Soluble Vitamins: The Induction of Growth-Promoting and Calcifying Properties in a Ration by Exposure to Ultra-Violet Light, *ibid.* **61**:405 (Sept.) 1924.

2. (a) Malmström, V.: Investigations Concerning the Influence of Light on Fat and Kindred Substances: Therapeutical Experiments with a Preparation Produced from Irradiated Cod-Liver-Oil, *Acta radiol.* **4**:173, 1925. (b) Villaret, M.; Justin-Besançon, L., and Fauvert, R.: Actinothérapie indirecte de la tuberculose, *Presse méd.* **34**:753 (June 16) 1926. (c) Bergmann, G. V.: Rachitis- und Tuberkulosebehandlung, *Deutsche med. Wochenschr.* **55**:1407 (Aug. 23) 1929.

3. (a) Levaditi, C., and Li, Y. P.: Étude expérimentale de la calcification des lésions tuberculeuses sous l'influence de l'ergostéral irradié, *Presse méd.* **38**: 168 (Feb. 5); 1720 (Dec. 17) 1930. (b) Spies, T. D.: The Calcification of Tubercles by Means of Irradiated Ergosterol, *Am. J. Path.* **6**:337 (May) 1930.

muscular weakness, headache, haziness of memory and numbness and tingling of the extremities.

The subjective symptoms are considered the most valuable index of tolerance or intolerance of therapy with large doses of vitamin D. The concomitant administration of calcium and phosphorus and exposure to solar or ultraviolet rays augment the effect of vitamin D and may thus render it more toxic.

#### COMMENT

Vitamin D in the form of cod liver oil has been one of the valuable adjuncts to the treatment of cutaneous tuberculosis for over a hundred years. In 1848 Emery<sup>19</sup> treated 74 patients with lupus vulgaris by administering cod liver oil. He employed up to one quart a day (100,000 units of vitamin D), but, although the results were excellent, the unpalatability of such large amounts of cod liver oil made the method impracticable.

The beneficial effects of generalized ultraviolet irradiation as employed in the treatment of lupus vulgaris by Heiberg and With and by Sequeira<sup>20</sup> may depend for their action on the conversion of the sterols in the skin into vitamin D or associated products.

Charpy insisted that the alcoholic solution of vitamin D<sub>2</sub> was more effective than a solution in oil. Both are good solvents for this vitamin, and neither oil nor alcohol is believed to produce any physical or chemical change in the vitamin. There is some indication that, unit for unit, the concentrated solutions have less antirachitic activity, and it may be that the alcoholic solution is more active because of its miscibility with the gastric contents. Unless dispensed in ampule form the volatility of the alcoholic solution would produce a concentration of the drug with resulting inaccuracy in dosage. Recently we have changed to a solution of vitamin D<sub>2</sub> in propylene glycol<sup>21</sup> which was especially prepared for us in a form containing 50,000 units per cubic centimeter. As propylene glycol is readily miscible with the gastric contents, it is felt that more beneficial results might be obtained with this vehicle.

Most of the French authors, including Charpy, administered calcium in addition to the vitamin. Dowling and Thomas<sup>14</sup> omitted calcium. We do not consider this supplementary calcium necessary if an adequate amount is contained in the diet (i. e., 1 quart of milk daily).

19. Emery, M.: Sur l'emploi de l'huile de foie de morue a haute dose dans le traitement du lupus, Bull. gén. de thérap. méd. et chir. 35:373, 1848.

20. Heiberg, K. A., and With, C.: Lupus Treated with General Carbon Arc-Light Baths as the Only Therapy, Brit. J. Dermat. 34:69 (March) 1922. Sequeira, J. H.: Carbon-Arc Light Baths in the Treatment of Lupus Vulgaris, ibid. 35:93 (March) 1923.

21. This preparation ("drisdol") was furnished by the Winthrop Chemical Company.

## BIOLOGIC EVALUATION OF VEHICLES FOR EXTERNAL APPLICATION OF BAL

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THE ORIGINAL work of Peters, Stocken and Thompson<sup>1</sup> demonstrated the great effectiveness of BAL (2,3-dimercaptopropanol) in saving animals systemically poisoned by liquid lewisite and showed the unequivocal benefits which resulted when BAL was applied externally to the skin contaminated by lewisite. Soon after these facts had been established, other research workers began to investigate such immediate practical problems as that of developing stable BAL preparations for topical application to the human skin and eye. It soon became obvious that the vehicle in which BAL was dissolved or suspended played an important role in determining the biologic efficacy and the physical and chemical stability of BAL. For this reason a large number and variety of vehicles had to be prepared and subjected to careful study.

After several groups of investigators had completed a considerable amount of preliminary work on different vehicles and on the technics for their testing, a cooperative program to study BAL preparations was set up by the "Subcommittee on Vehicles and Packages Suitable for BAL Ointments or Jellies for the Armed Forces,"<sup>2</sup> under the auspices of the Office for Scientific Research and Development. Members of the following groups cooperated in this program: (1) Committee on the Treat-

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The opinions and statements are the private ones of the authors and are not to be construed as those of the Navy Department or the naval service at large.

The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the Office of Scientific Research and Development and Cornell University Medical College.

Human volunteers for the tests carried out by the authors and described in this paper were made available through the United States Navy at United States Naval Hospital, Brooklyn; United States Naval Midshipmen's School, Columbia University, New York, and United States Naval Disciplinary Barracks, Hart's Island, N. Y.

1. Peters, R. A.; Stocken, L. A., and Thompson, R. H. S.: (a) 1941; (b) British Anti-Lewisite (BAL) Nature, London 156:616-619 (Nov. 24) 1945.

2. Sulzberger, M. B., 1943.

not occur by simple absorption, as in syphilis or sarcoidosis, but only by fibrosis and scarring. It seems logical, therefore, that a therapeutic agent which at first increases cellular metabolism and then produces cellular injury and calcification might favorably influence this existing equilibrium in favor of the scarring fibrotic type of healing which is so characteristic of lupus vulgaris. The selective affinity of tuberculous tissue for calcification was previously mentioned and seems important in explaining why normal tissues are not damaged with the employed dosage.

If in the future a deficiency of vitamin D or associated sterols is observed to have a bearing on the cause of cutaneous tuberculosis, some interesting facts may thereby be explained, such as the excessive incidence of the disease in northern European countries where the population is often subjected to diets which are deficient in vitamin D, phosphorus and calcium.<sup>26</sup> In other sections where this deficiency exists, an abundance of sunshine would offset the deficiency in diet. In all countries, however, there are a few persons who are unable to utilize vitamin D and calcium, as demonstrated by the occurrence of refractory rickets.

The onset of lupus vulgaris in childhood could also be explained in part by the increased requirement of the preadolescent for this vitamin as well as by his inability to store it in the body. Follis and his colleagues<sup>27</sup> reported that the postmortem examination of 230 children showed the presence of rickets in 46.5 per cent, whereas the presence of demonstrable vitamin D deficiency in adults is rare.

Many points need clarification before this therapy can be fully accepted. The initial enthusiasm of the French investigators may in time be modified. Our series is not large enough nor has sufficient time elapsed for any conclusions to be drawn other than to state that vitamin D therapy was definitely helpful in each case.

The rarity of the disease in America makes the accumulation of a large or controlled series difficult. We must look to European workers or to animal experimentation for the answer to such questions as (1) the most effective form of the vitamin or sterol (there are at least ten different substances which demonstrate antirachitic activity), (2) the best vehicle for the vitamin and (3) the advisability of administering calcium. In the meantime, the administration of vitamin D to patients with cutaneous tuberculosis in a dosage of 150,000 units daily constitutes, in our opinion, the most useful therapy available.

26. Hinglais, H., and Hinglais, M.: Remarques sur la carence grave du régime actuel en phosphore, calcium et vitamine D, *Presse méd.* 49:694 (June 25-28) 1941.

27. Follis, R. H., Jr.; Jackson, D.; Eliot, M. M., and Park E. A.: Prevalence of Rickets in Children Between Two and Fourteen Years of Age, *Am. J. Dis. Child.* 66:1 (July) 1943.

## CUTANEOUS REACTIONS TO PENICILLIN

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SINCE penicillin, in the process of its present day manufacture, takes substances from two sources, namely, the fungus Penicillium and the culture medium, which are known to be potential antigens, it would be reasonable to predict that penicillin would be capable of producing the same types of allergic reactions as would these parent substances. This prediction has come true in the experience of users of penicillin. It will be the purpose of this paper to correlate and to describe the various types of cutaneous reactions which have occurred in our practice and that of our colleagues.

### CONTACT DERMATITIS

As penicillin in the strengths usually applied to the skin in solutions or in ointments is not a primary cutaneous irritant, it should not, in theory, produce contact dermatitis when applied to skin which has not been sensitized by previous application of penicillin or by some other fungus.

Cohen and Pfaff<sup>1</sup> have reported that 0.95 per cent of normal patients who did not have a history of having used penicillin previously gave positive reactions to patch test with penicillin. If one believes the laws of dermatologic allergy, this would indicate that a small percentage of the general public has been sensitized by some previous fungous infection and can be expected to react when penicillin is first applied to their skin.

Binkley and Brockmole<sup>2</sup> were among the first to report contact dermatitis from penicillin. Their patient, a physician, experienced

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Read at the Sixty-Sixth Annual Meeting of the American Dermatological Association, Hot Springs, Va., June 12, 1946.

1. Cohen, T. M., and Pfaff, R. O.: Penicillin in Dermatologic Therapy: Report of Results in One Hundred Cases, Arch. Dermat. & Syph. 50:172-177 (March) 1945.

2. Binkley, G. W., and Brockmole, A.: Dermatitis From Penicillin: Report of Two Cases, Arch. Dermat. & Syph. 50:326-327 (Nov.) 1944.

### A. METHODS

The first and essential step was to develop testing methods which would permit evaluation of the relative efficacy of different BAL preparations against the effects of arsenical vesicants. It was hoped that these testing methods would be sensitive enough to demonstrate gross differences in efficacy.

#### I. TESTS ON RABBITS

Preliminary studies were carried out on rabbits, rats and guinea pigs. Rabbits, and in particular white rabbits, proved the most useful small laboratory animals for studying the effectiveness of BAL preparations. First, the skin of rabbits is highly susceptible to damage by lewisite and other arsenical vesicants; second, use of these animals permits the application of relatively large doses of arsenical vesicants to the skin, there being a considerable margin between the amounts producing damaging effects to the skin and those producing severe or lethal systemic effects on percutaneous absorption; third, the relatively wide expanse of the depilated belly or back of a full grown white rabbit permits application of equal and rather large amounts of the vesicant agent to symmetrically situated and widely separated sites. When fairly effective decontaminating and therapeutic materials are being dealt with, coalescence of the areas of damage is thus avoided, reciprocal interference between the lesions at the different sites reduced and the evaluation of the local damage facilitated.

Studies on lesions produced by these simultaneous applications in the same animal eliminate the errors due to such variables as individual susceptibility, age, state of health, diet, temperature and humidity. The following discussions of animal experiments are based largely on composite findings resulting from hundreds of experiments on several thousand rabbits.

**DESCRIPTION AND COURSE OF UNTREATED LEWISITE LESIONS IN RABBITS.**—Within a few minutes after application of approximately 2 mg. of liquid lewisite, the site of direct contamination begins to take on a pale, grayish or gray-brown, somewhat translucent appearance. This central zone is soon surrounded by a margin of edema and erythema, and often scattered satellite wheals and erythema appear in the adjacent regions.

No vesication is seen, but twenty-four to seventy-two hours after exposure the central zone consists of yellowish white or grayish brown

6. Sulzberger, M. B.; Baer, R. L., and Kanof, A.: Clinical Uses of 2,3-Dimercaptopropanol (BAL): Studies on the Toxicity of BAL on Percutaneous and Parenteral Administration, *J. Clin. Investigation* 25:474-479 (July) 1946.

7. Sulzberger, M. B.; Baer, R. L., and Kanof, A.: Clinical Uses of 2,3-Dimercaptopropanol (BAL): Skin Sensitization to BAL, *J. Clin. Investigation* 25:488-496 (July) 1946.

erythema nodosum type of reaction. Morris and Downing<sup>16</sup> reported severe bullous dermatitis in a patient four days after the last injection of penicillin. We have had 1 case of erythema multiforme with typical lesions on the backs of the hands and the forearms and a few lesions on the front of the thighs and the trunk after injection of penicillin.

Phytid types of reaction after injections of penicillin have been reported by others and have been seen by us. These reactions should be expected in view of Jadassohn's<sup>17</sup> observations that fungi contain specific and nonspecific antigenic fractions, which may sensitize a patient not only to the fungus with which he has been infected but also, parabiotically, to other fungi. Hence, theoretically at least, a patient who has had dermatophytosis of the feet or of the groin may suffer from a "-phytid" type of reaction if he is subsequently given penicillin.

Graves, Carpenter and Unangst<sup>18</sup> have reported 2 patients with histories of dermatitis of the hands, feet or groin and with positive reactions to trichophytin tests, who exhibited typical vesicular "id" reactions on the hands, feet or groin a few hours after each injection of penicillin. Lamb<sup>19</sup> reported 2 similar cases. We have seen this same sequence of events in 3 of our patients and shall discuss it from the industrial angle.

This "-phytid" type of reaction to penicillin has created a problem in the interpretation of industrial liability in certain cases. Dickson<sup>20</sup> referred to us a patient in whom cellulitis of the legs had developed after an industrial injury. Injections of penicillin were given for the cellulitis, whereupon the patient experienced severe vesicular dermatitis of the feet, which had formerly been the site of dermatophytosis but which had been normal at the time of injury. Inasmuch as this dermatophytosis of the feet was secondary to treatment necessary for an industrial injury, it was interpreted by us as industrial in origin and was so accepted by the insurance company. Dickson reported that he had had 3 other similar cases. We have seen, and other physicians have reported to us, mild erythematous reactions in the crural area. These, presumably, may be "ids" at the site of former crural fungous infections.

16. Morris, G. E., and Downing, J. G.: Bullous Dermatitis (Dermatitis Medicamentosa) from Penicillin, *J. A. M. A.* **127**:711 (March 24) 1945.

17. Jadassohn, W.; Schaaf, F., and Wohler, G.: Analyses of Composite Antigens by Schultz-Dale Technique: Further Experimental Analysis of Trichophytons, *J. Immunol.* **32**:203-227 (March) 1937.

18. Graves, W. N.; Carpenter, C. C., and Unangst, R. W.: Recurrent Vesicular Eruptions Appearing During Administration of Penicillin, *Arch. Dermat. & Syph.* **50**:6-7 (July) 1944.

19. Lamb, J. H.: Allergic Reactions During the Administration of Penicillin, *Arch. Dermat. & Syph.* **52**:93-95 (Aug.) 1945.

20. Dickson, D.: Personal communication to the authors.

tions of penicillin in patients being treated for dermatoses than in non-dermatologic patients receiving the injections (6 per cent). This coincides with our experience. We believe that penicillin should not be applied to the skin or injected into patients with certain exudative dermatoses, such as eczema or eczematoid dermatitis, unless there is a clearcut indication for its use, such as superimposed pyogenic infection which has not yielded to older conservative therapy.

#### MISCELLANEOUS REACTIONS

Miller<sup>24</sup> has reported 4 severe toxic erythema eruptions in patients who were given penicillin orally. He commented on the delayed appearance of the eruption after ten to fourteen days. Maynard<sup>25</sup> told us of a patient who experienced dermatitis around the site of a deltoid muscle into which penicillin in wax and oil had been injected. The arm became edematous from shoulder to wrist.

#### EXPERIMENTAL STUDIES

Divergent observations have been reported by those who have studied persons reacting to penicillin and normal persons by means of patch, scratch and intradermal tests. As mentioned, Cohen and Pfaff<sup>1</sup> obtained positive reactions to patch tests in 0.95 per cent of normal persons who had never been exposed to penicillin. Most authors have noted positive reactions to patch tests in patients who had contact dermatitis from penicillin. Rostenberg and Welch<sup>26</sup> found tuberculin type of reactions to intradermal injections of penicillin in 5.5 per cent of 144 normal persons who had not had penicillin previously. They were unable to demonstrate circulating antibodies in these persons or in 1 patient with urticaria from penicillin by means of the Prausnitz-Küstner test. The experiments of McGuire<sup>27</sup> suggested a positive transfer of antibodies.

We obtained blood serum from 5 patients who had experienced urticaria after injections of penicillin. The following experiments were performed:

EXPERIMENT 1.—Four female patients received intradermal injections of 0.1 cc. of serum from the 5 urticarial reactors with 0.1 cc. of normal serum as a control. Forty-eight hours later they received intramuscular injections of a single dose of 200,000 units of penicillin in sesame oil. The areas where the serums from persons with urticarial reactions had been injected were observed in twenty-four and in forty-eight hours but reactions were not seen at any of the sites.

24. Miller, H.: Personal communication to the authors.
25. Maynard, M. T.-R.: Personal communication to the authors.
26. Rostenberg, A., Jr., and Welch, H.: A Study of the Types of Hypersensitivity Induced by Penicillin, *Am. J. M. Sc.* **210**:158-167 (Aug.) 1945.
27. McGuire, J. A.: Localized Sensitivity to Crude Penicillin: Report of a Case, *Arch. Dermat. & Syph.* **53**:31-33 (Jan.) 1946.

TESTS ON TREATMENT AND DECONTAMINATION.—*Preparation of Test Sites.*—The bellies of rabbits are depilated with a strontium or barium sulfide paste. The rabbits are tied down on the usual type of animal boards, and the symmetrically situated cutaneous sites are marked with a rubber stamp outlining a ring about 3 cm. in diameter. The sites are so chosen that with the animal securely tied each selected site forms as nearly as possible a horizontal plane surface. The tendency to "running" or irregular spread of the droplet is thereby reduced.

When the effect of a single BAL preparation is to be compared with the result at an untreated control site, two symmetrically situated sites are marked, one on each flank and as far apart as feasible. When two BAL preparations are to be compared, one site on each flank is used for each agent; an untreated control site may then be placed asymmetrically and anteriorly, well away from the sites on the flanks. When three or more BAL preparations are to be compared, two symmetrically placed sites are chosen anteriorly and two posteriorly.

The positions used for the respective agents are varied from animal to animal in order to eliminate any errors which might possibly arise from differences in susceptibility anteriorly and posteriorly. In our experience, no significant differences in susceptibility of the anterior and posterior sites could be noted. However, the presence of even small amounts of hair, of abrasions, etc., may modify the effects of the vesicant and the treatment agent. For this reason depilation must be uniform and as perfect and complete as possible.

*Application of Vesicant.*—After the selected sites have been marked, a measured amount of liquid vesicant is dropped on the skin in the center of the stamped ring. About 1.6 to 2.0 mg. of lewisite has been found to be well suited for the testing of BAL materials. The measurement and distribution of the vesicant are accomplished with a microsyringe.

*Application of BAL Preparations.*—After chosen identical intervals of time, which are precisely measured with a stop-watch according to a planned schedule, the agents to be investigated are applied in equal measured amounts to each contaminated area. In the case of treatment with ointments, creams, jellies or similar preparations amounts of 0.1 cc. to 0.05 cc. are usually optimal. In the case of liquids 5 drops as delivered by a 27 gage needle is generally a suitable amount. The treatment agent is gently rubbed into the contaminated area and into the entire zone encircled by the stamped ring, a smooth-tipped glass stirring rod being used for thirty seconds. On completion of the application for treatment, the animals are left tied down for about one-half hour more and then released and returned to their cages.

In different series of experiments, the intervals of time between application of vesicant and application of treatment agent varied between three minutes and two hours. In the case of various BAL ointments and other preparations of BAL, the optimal interval, i. e., that which was best suited to bring out most sharply any differences in therapeutic effectiveness, was found to be thirty minutes to one hour.

No less than 6 and sometimes, in crucial experiments among close contenders, as many as 60 or more animals were used for each comparison.

*Reading and Evaluation of Results.*—The readings are usually made at arbitrary intervals after the applications, preferably beginning at forty-eight or seventy-two hours and continuing until a week or ten days

4. Because of its ability to sensitize, penicillin should not be used indiscriminately by dermatologists. In general, its use should be avoided in noninfectious dermatoses. When used with an understanding of its limitations and of its dangers penicillin is valuable in the treatment of certain pyogenic infections of the skin.

3115 Webster Street.

#### ABSTRACT OF DISCUSSION

DR. CORNELIUS F. LEHMAN, San Antonio, Texas: The first examples of any note of sensitivity to penicillin that I saw were in a general hospital in England in the early part of 1945. These were in about 20 patients who were in the same convoy and who had received, at the time of the secondary closure of wounds, a resumption of penicillin therapy, the primary treatment having been given about three weeks previously as first aid in the forward stations.

My colleagues and I thought then that reactions to such an inert substance were out of the question, and penicillin at first was not blamed. I searched for some other common denominator, such as food. Then I administered a dose of penicillin to a volunteer. In a few hours his urticaria came back with severe angioneurotic edema, which necessitated splitting the cast on his arm, and a painful swelling of the knees and the ankles.

Since then we have been on the lookout for reactions and have discovered that penicillin sensitivity is rather common. The remarkable thing, to me, is that of the thousands of doses of penicillin which were used in the army early in the war so few cases of sensitization were noted. I am sure that that was not because they were overlooked, since when a severe reaction to penicillin develops the patient will tell the physicians about it.

I often have wondered why there are more reactions to penicillin now than were seen earlier in the army, and whether the increase is due to a change in the manufactured product or whether we have a different type of patient with different barometric pressure, heat, humidity and other factors.

I have seen 2 cases of exfoliative dermatitis. "Benadryl hydrochloride" N.N.R. (diphenhydramine hydrochloride) has been used with varying results but was not helpful in these 2 cases of exfoliative dermatitis. I have seen a severe reaction with urticaria and angioneurotic edema in a physician, which appeared nine days after the use of penicillin lozenges. In his case a few previous treatments with penicillin spray had probably resulted in sensitization.

To explain the reactions I have frequently tested patients after their recovery with the refined penicillin broth and with trichophytin, and as yet I have not found any explanation that is satisfactory.

I think that the commonest sensitizer will eventually prove to be epidermophytin, particularly in cases of the inflammatory type. Following this hypothesis, I would not be surprised if in the future many cases of violent attacks of asthma after penicillin therapy should occur, particularly in patients with preexisting fungous infections of the lung or the skin.

DR. RICHARD S. WEISS, St. Louis: The most violent reaction to the use of a drug that I have ever seen was in a physician who used penicillin mist for sinusitis. His face was swollen to about twice the normal size; he had fever; he was exceedingly ill. The cause of the disorder was not suspected. It was thought that he had erysipelas, and he was given penicillin intramuscularly. On discovery of the cause he stopped the use of penicillin and recovered in three or four days.

that this ointment may irritate when left over the week end. Patients to whom penicillin ointment is given on Monday or Tuesday will sometimes be irritated, whereas patients to whom the ointment is given in the middle of the week, when it was freshly made, do not have irritation.

DR. MARTIN T. VAN STUDDIFORD, New Orleans: In the Marine Hospital penicillin was used for patients with gonorrhea. Some of these patients had had two or three courses of penicillin therapy at different places. One young man experienced a severe reaction from penicillin. After two weeks an intern applied a patch test on the patient's arm; edema of the epiglottis resulted. Only with a great deal of effort was a tracheotomy avoided.

The most peculiar reaction to penicillin that I have seen was in a sailor with a big ship tattooed on his chest. He had an urticarial rash in some of the tattoo marks. He was sensitive about his tattoo and would not let us take a section or a picture. I should like to have known what chemical was embedded in his skin that would have given him that reaction.

DR. FRANK C. COMBES, New York: One reaction accompanying the administration of penicillin has not been mentioned, and I think it is one which we should take into consideration. What reaction will follow the administration of penicillin in beeswax? What is going to happen to the beeswax?

A number of years ago a group of us injected into the arms of some patients epinephrine in beeswax to produce slow absorption. Two or three years afterward lumps developed around the wrists of these patients and on the backs of their hands. The beeswax had not been absorbed. It had gradually worked down the fascial planes, and in some instances it was necessary to remove the beeswax surgically.

Many reactions to penicillin, I think, depend on dosage. It is possible that at present the use of penicillin is more or less experimental. It is possible that in larger doses it would be more effective. I know of a severe reaction to penicillin in a patient with ocular pemphigus, an acute fulminating type of disease. In view of the good results obtained from large doses in bacterial endocarditis, we gave this patient 1,000,000 units a day. After four or five days she experienced severe angioneurotic edema. I do not believe that I have ever seen such collections of fluid in the joints, and the patient suffered excruciating pain. That was after she had received 6,000,000 units in six days.

I agree with Dr. Engman in some respects regarding the topical application of penicillin. We have discontinued penicillin as an ointment in the formulary of Bellevue Hospital, for which there are several reasons. Dr. Engman has already mentioned one. The other is the difficulty of finding a base which is relatively stable. However, I will say that penicillin in powder form in polyethylene glycol dispersion is the finest treatment which I know for impetigo. There is nothing which remotely approaches the rapidity with which impetigo responds to it. In some cases severe lesions will disappear after two or three applications, within twelve hours. The lesions will dry up, and it is unusual for any case to persist more than three or four days. Penicillin powder is irritating, but in polyethylene glycol it is nonirritating and is slowly liberated. Polyethylene glycol is soluble in serum, and the results are excellent.

DR. GEORGE M. LEWIS, New York: Acting on our own clinical observations, which corroborate the observations of Dr. Templeton and Dr. Wile, that dermatophytid and sometimes dermatophytosis-like reactions occur after administration of penicillin, my colleagues and I instituted a short series of experiments with animals which will be reported before the Society of Investigative Dermatology.

*Effect of 5 Per Cent BAL preparations in Protection against Lewisite.*

—With the experimental technic described, it could be shown that certain preparations containing BAL in 5 per cent concentration afforded significant protection against approximately 2 mg. of liquid lewisite. This protective effect was clearly demonstrable for thirty minutes and even one hour after BAL application.

## II. TESTS ON HUMAN BEINGS

Because of the well known differences in the structure and responses of the animal and human skin, all BAL materials which appeared promising in tests on rabbits were further tested in human subjects. In our

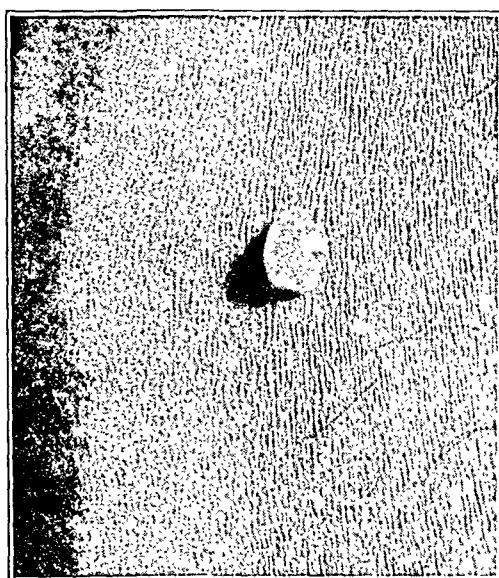


Fig. 2.—A tense, clear vesicle on human skin forty-eight hours after application of a small dose of liquid lewisite.

particular studies such repetition of the assays on human skin was especially necessary, because the rabbit's skin lacks the capacity of human skin to vesicate after contamination with lewisite.

In the tests on human volunteers, we again employed the method used on rabbits, namely, that of paired comparisons at symmetrically situated cutaneous sites. Through studies on symmetric lesions produced by simultaneous applications in the same human subject, we eliminated the errors due to such variables as individual susceptibility, age, state of health, diet, temperature, humidity and physical activities. The subsequent discussions of experiments on human subjects are based largely on composite findings resulting from many experiments on several hundred volunteers.

A group of 129 patients exhibiting clinical evidence of primary or secondary syphilis was treated with 10,000,000 units of penicillin, administered by intravenous drip over a twenty-four hour period, from March 28 to Aug. 2, 1945. All revealed lesions which on dark field examination were positive for *Treponema pallidum*.

The ages of the patients ranged from 15 to 48 years: 62 per cent were 25 or under; 80.7 were 30 or under. Of these patients 119 were previously untreated for syphilis. The remaining 10 had received varying amounts of arsenical and bismuth preparations and subsequently exhibited clinical and laboratory evidence of relapse or had failed to show negative results on dark field examination.

Eligibility for treatment was determined on the basis of freedom from detectable pathologic changes of the cardiovascular, pulmonary, urinary and hemopoietic systems. Electrocardiograms and roentgenograms taken at a distance of 2 meters were included in the pretreatment medical survey. Examinations of cerebrospinal fluid were performed routinely before treatment.

The administration of penicillin by the intravenous drip technic is known to cause thrombophlebitis<sup>7</sup>; therefore an attempt was made to circumvent this complication by the use of the anticoagulant heparin, incorporated in the "Pitkin menstruum."<sup>8</sup> Three hundred milligrams of heparin was injected subcutaneously into the anterolateral aspect of the thigh immediately before the patients were given the intravenous drip by the usual technic, the veins of the forearms being utilized. The rate of flow of the solution was regulated by means of a pinch clamp to deliver 1,000 cc. of solution continuously over a twenty-four hour period. The levels of penicillin in the blood and cerebrospinal fluid as previously reported<sup>6</sup> were determined by the method described by Rosenblatt, Altur-Werber, Kashdan and Loewe.<sup>9</sup>

Further treatment was not given unless clinical or serologic relapse or pregnancy occurred. The last patient treated received therapy on Aug. 2, 1945. Therefore the maximal period of observation ranges from seven to eleven months.

7 Anderson, G. D.: The Treatment of Infections with Penicillin, *New England J. Med.* **232**:400 (April 5) 1945. Keefer, C. S.; Blake, F. G.; Marshall, E. J., Jr.; Lockwood, J. S., and Wood, W. B., Jr.: Penicillin in the Treatment of Infections: Report of Five Hundred Cases, *J. A. M. A.* **122**:1217 (Aug. 28) 1943.

8. Loewe, L., and Rosenblatt, P.: A New Practical Method for Subcutaneous Administration of Heparin: Preliminary Report, *Am. J. M. Sc.* **208**:54 (July) 1944.

9. Rosenblatt, P.; Altur-Werber, E.; Kashdan, F., and Loewe, L.: A Method for the Determination of Penicillin Levels in Body Fluids, *J. Bact.* **48**:599 (Nov.) 1944.

**DESCRIPTION AND COURSE OF UNTREATED LEWISITE LESIONS IN HUMAN SUBJECTS.**—When about 2 mg. of liquid lewisite is placed on the human skin, the untreated lesions take approximately the following course:

Within a few minutes after application of the droplet, a local wheal and erythema ensue. The speed of development of these changes appears to be somewhat dependent on the peculiarities of the person and of the cutaneous site and is also influenced by the prevailing temperature and the relative humidity (being accelerated and intensified at higher temperatures and humidities).

Within the next twenty-four hours, depending on individual and local susceptibility and temperature and humidity, a vesicle surrounded by a halo of erythema appears and is usually fully developed in twenty-four hours. At first the vesicle may be tense and the contents clear (fig. 2), but it soon becomes flaccid and its contents become first cloudy and then often brownish and bloody. Within the next day or two the vesicle breaks or dries to form a dark brown, rather thin and superficial crust.

During this period the central lesion is normally surrounded by an area of erythema and edema. In five to eight days the crust comes off and reveals a superficial ulcer or defect which heals without much contracture, leaving a rather soft scar.

Healing is generally complete within two and a half to four weeks. Though most of the untreated lesions are obviously contaminated by the ordinary, practically ubiquitous micro-organisms, there is relatively little tendency to progressive or deep, invasive infection.

**TESTS OF TREATMENT AND DECONTAMINATION.—Preparation of Test Sites.**—As stated, the technic follows closely that described for rabbits. The otherwise unprepared flexor surfaces of the forearms are used. Symmetrically situated sites are marked with a rubber stamp 3 cm. in diameter. The sites are selected so that their surfaces lie as nearly as possible in a horizontal plane. The tendency to "running" or irregular spread of the droplet is thereby reduced.

When the effect of a single decontaminating agent is to be compared with the result at an untreated control site, two symmetrically situated sites are marked, one in the center of the flexor aspect of each forearm. When two agents are to be compared, one site on each forearm is used for each agent. In the rare instances in which an untreated control site appears essential, such a site may then be placed asymmetrically, distally or proximally on the flexor aspect of one forearm, well away from the other site on the same forearm. When three or four agents are compared, two symmetrically placed sites are chosen proximally and two distally.<sup>12</sup>

In tests involving more than two sites, the positions used for the respective agents are varied from subject to subject in order to eliminate any errors which

12. Untreated control sites or comparison of three or four treatment agents in human subjects were used only when the treatment agents to be tested were known to be sufficiently effective to preclude dangerous degrees of damage.

It is worthy of comment that schemes of treatment employing as little penicillin as 600,000 units in seven and one-half days<sup>10</sup> or 1,200,000 units in three and three-quarters days<sup>11</sup> yielded significantly superior results than the large dose of 10,000,000 units over a twenty-four hour period given intravenously in this series.

As might have been anticipated, results were better for patients with seronegative primary syphilis than for those with either seropositive primary or secondary syphilis. Thus, of 15 patients presenting seronegative primary syphilis, only 5 (33.3 per cent) relapsed at the end of seven months. Of 29 patients with seropositive primary syphilis who were treated, 13 (44.8 per cent) relapsed at the end of seven months, and of 85 patients with secondary syphilis 43 (50.6 per cent) relapsed.

#### SUMMARY

1. One hundred and twenty-nine patients who were found on dark field examination to have primary or secondary syphilis were treated with 10,000,000 units of sodium penicillin intravenously over a twenty-four hour period.
2. Ten million units of penicillin given intravenously in a twenty-four hour period in this series proved to be grossly inadequate in the therapy of early syphilis.

Mr. John L. Smith, of Charles Pfizer and Co., Inc., showed keen interest and gave valuable suggestions and constant cooperation. Through him we obtained the generous supply of penicillin utilized in these experimental studies. Dr. H. C. McCraney and Dr. Lydia Marshak gave assistance, and the technical work of Elsie Miller, B.A.; Ellen Bienfang, R.N., and Mary Gleason made this study possible.

54 West Hubbard Street.

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10. Bauer, T. J.; Bundesen, H. N.; Craig, R. M.; Schwemlein, G. X., and Barton, R. L.: The Treatment of Early Syphilis with 600,000 Units of Penicillin in Seven and One-Half Days, *Am. J. Syph., Gonor. & Ven. Dis.* **31**:45 (Jan.) 1947.
  11. Craig, R. M.; Schwemlein, G. X.; Barton, R. L.; Bauer, T. J., and Bundesen, H. N.: Penicillin in the Treatment of Early Syphilis: Four Hundred and Twenty-Nine Patients Treated with 1,200,000 Units in Ninety Hours, to be published

might possibly arise from differences in susceptibility proximally and distally. In our experience, no significant differences in susceptibility of the proximal and distal sites could be noted.

*Application of Vesicant and of Treatment Agents.*—The application of the vesicant and treatment agents is carried out in a manner similar to that described for tests in rabbits.

For at least thirty minutes after the completion of the treatment, all subjects must keep their forearms in horizontal position with flexor surfaces up and must avoid all wiping or other disturbance of the sites of the test.

In different series of experiments the intervals of time between application of vesicant and application of treatment agents varied from three minutes to two hours. The optimal interval for the different ointments and other preparations of BAL was found to be thirty to sixty minutes. No less than 6 and sometimes, in crucial experiments, as many as 24 subjects were used for each comparison of the effectiveness of two different preparations of BAL.

*Reading and Evaluation of Results.*—The readings are usually made at forty-eight hours and one week; in crucial experiments the lesions are observed until healing has taken place. Again, as in the experiments on animals, clinical evaluation and clinical description have proved to be the most efficient method of evaluation in human subjects.

*Effect of 5 Per Cent BAL Preparation on Lewisite Lesions in Human Beings.*—BAL applied locally in 5 per cent or greater concentration distinctly modified and reduced the damage produced by lewisite in the human skin. With small doses of lewisite, vesication and necrosis could often be completely inhibited by application of the BAL preparation within fifteen minutes to two hours after application of the vesicant. The damage produced by 2 mg. doses of liquid lewisite was distinctly reduced by application of the BAL preparation at time periods of from two minutes to fifteen minutes after application of the vesicant.

**TESTS OF PROTECTION.**—The studies on protection are carried out by reversing the procedure described under "Treatment and Decontamination" in a manner similar to that specified in tests on animals, i. e., by applying the vesicant after the application of BAL.

*Effect of 5 Per Cent BAL Preparations in Protection Against Lewisite.*—It could be shown that certain preparations containing BAL in 5 per cent concentration afford as great a degree of protection against small doses of liquid lewisite on human skin as they do against larger doses on the skin of rabbits. No tests were made on protection afforded against larger doses of liquid vesicant on human skin.

#### B. VEHICLES

The BAL preparations originally studied by us had included ointments, pastes, emulsions, solutions, suspensions, watery jellies, "shake lotions" and powdery suspensions. Based on these preliminary investigations, the following categories of BAL preparations were selected,

of normal rabbits varies from 0 to 60 units, while the total acidity varies from 122 to 213 units, the units being in terms of cubic centimeters of decinormal sodium hydroxide required for the neutralization of the free hydrochloric and total acids per hundred grams of stomach contents. Under the conditions it was thought that the simultaneous administration of 0.2 Gm. of anhydrous sodium citrate with each dose of penicillin was sufficient.

Serum assays employing hemolytic *Staphylococcus aureus* (H) were conducted with blood removed one hour after the second and eighth doses.

#### RESULTS OBSERVED

As shown in the table, 3 rabbits were employed for each dose of penicillin, the doses per kilogram of weight being 500, 1,000, 5,000, 10,000, 15,000 and 20,000 units. It will be observed that all 3 rabbits given 500 units per kilogram per dose for thirty doses, totaling 15,000 units, showed temporarily negative results on dark field examinations but that all relapsed and gave positive results on transfer of lymph nodes. One hour after the second dose the serum assays showed approximately 0.5 unit per cubic centimeter, and they showed 0.5 to 1.0 unit per cubic centimeter an hour after the eighth dose.

All 3 rabbits given 1,000 units per kilogram per dose for twenty-one to thirty doses, totaling 21,000 to 30,000 units, gave negative results on dark field examination, but 2 of the rabbits surviving forty-nine days showed positive results on transfer of lymph nodes. One hour after the second dose serum assays showed 0.25 to 0.51 unit per cubic centimeter, and they showed about 1.0 unit per cubic centimeter one hour after the eighth dose.

All 3 rabbits given 5,000 units per kilogram per dose for thirty doses, totaling 150,000 units, gave negative results on dark field examination, but all showed positive results on transfer of lymph nodes. Serum assays of blood removed one hour after the second dose showed about 0.51 unit per cubic centimeter, and they showed from 0.25 to 0.5 unit one hour after the eighth dose.

Three rabbits given 10,000 units per kilogram per dose for thirty doses, totaling 300,000 units, gave negative results on dark field examination, but all showed positive results on transfer of lymph nodes. Serum assays conducted with blood removed one hour after the second dose showed 0.51 to 2.0 units per cubic centimeter, and they showed 0.5 to 1.0 unit per cubic centimeter one hour after the eighth dose.

Three rabbits given 15,000 units per kilogram per dose for thirty doses, totaling 450,000 units, showed negative results on dark field examination and 1 of these showed a negative results on transfer of lymph nodes. Two rabbits given 20,000 units per kilogram per dose,

made up and studied by means of an organized and integrated program of testing under the auspices of the Office of Scientific Research and Development<sup>13</sup>: (1) water-soluble gum bases (containing, e. g., tragacanth or methyl cellulose); (2) grease bases (containing, e. g., anhydrous wool fat, petrolatum, peanut oil, white wax or aquaphor); (3) vanishing cream type bases (containing, e. g., cetyl alcohol or stearic acid), and (4) nonaqueous water-soluble bases (containing, e. g., Carbowax or mannitol and dextrin).

Seventeen preparations belonging to the aforementioned categories were filled in selected lead tubes and subjected to the following standard tests for physical properties and chemical stability by the pharmaceutical groups previously listed<sup>3</sup>: (1) tests for deterioration after freezing, thawing and heating; (2) tests for deterioration on storage in alternating high and low temperatures; (3) tests for deterioration in long term storage (cold room storage or shelf storage); (4) tests for "workability" in cold weather (viscosity, malleability, etc.), and (5) tests for corrosion and other effects on tubes.

The preparations which proved satisfactory in these standard tests for physical properties and chemical stability were then subjected to the foregoing outlined standard biologic tests for relative efficacy in decontamination, treatment and protection.

**TESTS.**—Each of the preparations was tested as follows: A. Against liquid lewisite on rabbits were used: (1) a freshly prepared sample vs. a standard uniform and common control consisting of 5 per cent BAL in KY Jelly and (2) a freshly prepared sample vs. samples aged by freezing and thawing and by shelf storage. B. Selected preparations were then tested, the same type of controls being used for decontaminating and therapeutic efficacy (and in some instances also for protective efficacy) against liquid lewisite on human skin. C. While all these tests were by indirect comparisons through a common control agent, as a final check samples of the best preparations were directly compared with each other in symmetric sites in human subjects.

**RESULTS.**—*A. Decontamination and Treatment.*—In general the tests for decontamination and treatment efficacy showed only small differences in effectiveness between preparations containing 5 per cent BAL in many different vehicles. Thus, for example, 5 per cent BAL in KY jelly appeared to be slightly more effective than many of the other 5 per cent BAL preparations tested. It appears possible that these differences were within the range of error of the method. The lack of significant differences may have been due to the fact that our tests for biologic evaluation of preparations for decontamination and treatment either were not sensitive enough to detect relatively small differences

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13. Sulzberger,<sup>2</sup> Lazier,<sup>3</sup>

## PRENATAL SYPHILIS

Its Prevention by Use of Penicillin in Treatment of Pregnant Women  
with Early Infectious Syphilis

HANS C. S. ARON, M.D.

ROBERT L. BARTON, M.D.

AND

THEODORE J. BAUER, M.D.\*  
CHICAGO

TWO REPORTS have been published recently,<sup>1</sup> showing spectacularly favorable results in the prevention of prenatal syphilis with the use of penicillin in the treatment of syphilitic pregnant women. It is well known that mothers with syphilis which is beyond the infectious state may deliver normal nonsyphilitic children in a varying but large percentage of cases. Transmission of syphilis to the fetus occurs much more frequently when pregnant women have syphilis in the early infectious stages than in the later stages of the disease. The efficacy of any therapeutic procedure in preventing prenatal syphilis, therefore, will be evaluated most reliably by the effect on the offspring of mothers who during pregnancy had indisputable early infectious syphilis.

When rigidly selected, the number of patients whom we saw who had proved infectious syphilis during pregnancy was limited. To obtain a satisfactory number of cases for evaluation it is necessary to compile the studies which have been made at various institutions.

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From the Chicago Intensive Treatment Center, Venereal Disease Control Program, Chicago Board of Health in cooperation with the United States Public Health Service.

The work described in this paper was done under a contract, recommended by the Committee on Medical Research, between the office of Scientific Research and Development and the Chicago Intensive Treatment Center.

1. (a) Ingraham, N. R.; Stokes, J. H.; Beerman, H.; Lentz, J. W., and Wammock, V. S.: Penicillin in the Syphilitic Pregnant Woman, J.A.M.A. **130**:683 (March 16) 1946. (b) Goodwin, M. S., and Moore, J. E.: Penicillin in the Prevention of Prenatal Syphilis, *ibid.* **130**:688 (March 16) 1946.

in efficacy—or perhaps regardless of the differences in the amount or rate of delivery of BAL from the different vehicles, it was in each case in excess of that needed for the quantitative neutralization of all the lewisite applied.

There is good evidence that the methods used were incapable of showing differences of less than 1.25 per cent of BAL, for in repeated tests it was shown that an aged 5 per cent BAL preparation, which according to chemical analyses had lost up to 25 per cent of its BAL content,

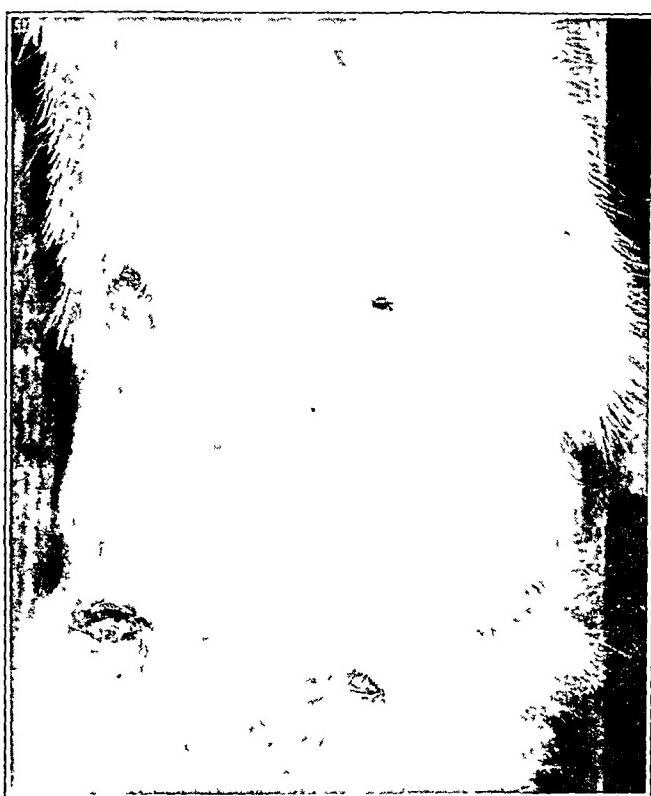


Fig. 3.—Rabbit's belly three weeks after application of approximately 1.6 mg. of liquid lewisite to each of four sites. Thirty minutes after vesicant exposure, the site at the upper right of the picture was treated with 10 per cent BAL in thiodiglycol; at the lower right, with dichloramine T 20 per cent in triacetin, and at the upper left with 8 per cent hydrogen peroxide in water; the site at the lower left is the untreated control. Note the large adherent dark crust at the untreated site and the superiority of BAL over the two other agents.

was just as effective in decontamination and treatment as was the same freshly made preparation with its full 5 per cent content of BAL. On the other hand, the methods of biologic evaluation were fully adequate to demonstrate differences in efficacy of decontamination and treatment when the 5 per cent BAL preparations were compared with all the older decontaminating agents which did not contain BAL (fig. 3).

group of 28 women with infectious syphilis during pregnancy who (before the advent of penicillin) had received intensive arsenotherapy (form of treatment described by Eagle and Hogan, that of Schoch or fever chemotherapy).<sup>2</sup> These patients came from the same socio-economic level, had the same racial origin and were selected for early infectious syphilis by the same criteria as were the patients in the penicillin group.

The results of this Chicago arsenical group, therefore, are strictly comparable to the results of the Chicago penicillin group. Tabulated side by side, they give the second opportunity for comparing the results

TABLE 1.—Number of Infants Examined and Results of Treatment

Group	Type of Treatment	Number of Infants Born	Infants Born Alive, Apparently Normal		Infants Born Alive, Normal at Follow-Up		
			Infants with Syphilis	(1 stillborn)	Physical	Roentgenologic	Serologic
Philadelphia	Penicillin.....	27*	26	1	26	26	26
Baltimore	Penicillin.....	33†	33	0	33	All examined	33
Chicago	Penicillin.....	36‡	34	0 (1 stillborn)	34	All examined	33
Total.....		96	93	1 and 1 stillborn; probably syphilitic	93		92
Chicago							
Modified form described by Eagle and Hogan .....		18	18§	2	18	15	18
Fever; 6 hr., temp. 106 F. (r.), 60 mg. oxophenarsine hydrochloride, 150 mg. bismuth compound.....		6	6	1	6¶	5¶	6¶
1,080 to 1,200 mg. oxophenarsine over 8 to 14 days (Schoch).....		4	4#	0	4	3	4
Total (intensive arsenotherapy)...		28	28	3	28	23	28

\* One died at 7 months of age of acute febrile illness; no evidence of syphilis on autopsy. One mother had two pregnancies, the second infant not included because mother was not infectious.

† One died at 19 weeks of acute nutritional disturbance and sickle cell anemia but was seronegative in reaction.

‡ One died of prolapse of cord and asphyxia; no autopsy; 1 was stillborn.

§ One mother had another child thirteen months after Eagle treatment. At age of 5 months infant's Kahn reaction was negative, and the child was normal on physical examination (not inserted in table).

|| Two infants with congenital syphilis were included.

¶ One infant with congenital syphilis was included.

# One mother delivered another child two years after Schoch therapy. At age of 8 weeks infant's Kahn reaction was negative and physical and roentgenologic examinations showed no abnormalities (not inserted in table).

of treatment with penicillin and intensive arsenical therapy during pregnancy in preventing prenatal syphilis.

In the Chicago group, of the 36 infants who were delivered of mothers whose syphilis was treated with penicillin exclusively, 1 died of

2. Bundesen, H. N.; Bauer, T. J., and Kendell, H. W.: The Intensive Treatment of Gonorrhea and Syphilis, *J.A.M.A.* **123**:816 (Nov. 27) 1943.

The sum of the biologic tests on decontamination and treatment as well as the physical and chemical tests showed that the two formulas designated as A and B not only were physically and chemically by far the most stable and desirable, but were also fully as effective as any other BAL preparations in their decontaminating and therapeutic effects against liquid lewisite on both rabbits' and human skin.

	Per Cent
Peanut oil .....	36.95
Wool fat, anhydrous .....	8.0
Cetyl alcohol .....	10.0
Glyceryl monostearate .....	10.0
White petrolatum, soft .....	25.0
Benzyl benzoate .....	5.0
Mixed tocopherols (40%) .....	0.05
<b>BAL .....</b>	<b>5.0</b>
 Formula B:	
Boric acid .....	1.898
Carbowax 4000 .....	7.592
Carbowax 1500 .....	47.45
Ethylene glycol .....	37.96
Isoascorbic acid .....	0.05
Thiamine hydrochloride .....	0.05
<b>BAL .....</b>	<b>5.0</b>

Moreover, these two preparations were shown to be among the most effective<sup>4</sup> in counteracting damage by lewisite in rabbits' eyes. On the basis of all these results the armed forces selected formulas A and B as the most satisfactory for issue to American military personnel. Early in 1943 the United States Navy selected formula A for individual issue and use against arsenical vesicant contamination in the eye and on the skin, and in April 1943 the United States Army selected formula B for individual ophthalmic issue and supplied it also in field chests and kits for use on the skin.

*B. Protection.*—It is noteworthy that the degree and duration of protection varied greatly with the type of vehicle in which BAL was incorporated (fig. 4) and that this was in sharp distinction to the relative lack of influence of the vehicle on the decontaminating and therapeutic efficacy of 5 per cent BAL preparations. Thus there was no obligatory correlation between superiority of a certain vehicle as protective agent and its effectiveness in decontamination and treatment. There is as yet no knowledge as to the precise reasons for these decided differences in the protective effect of BAL when incorporated in different vehicles.

Among the vehicles studied, protection was relatively poor with BAL in petrolatum, zinc oxide-talcum-water-glycerin "shake" lotion, vanishing cream, methyl cellulose jelly, sodium alginate jelly, thioglycol and several of the grease bases. The greatest protection was observed with equivalent concentrations of BAL in the formulas A, B, KY jelly and a mannitol-dextrin base. The photograph (fig. 5) is characteristic of the protective effects which can be achieved through the external application of BAL preparations.

premature infants was 9.4 per cent with the highest incidence of 10.2 per cent in 1930 and the lowest of 7.5 per cent in 1933. The incidence of prematurity in our series of mothers who were treated with penicillin was 8.8 per cent. No case of abortion or miscarriage was reported in our series of women who were treated with penicillin during pregnancy. This problem requires evaluation at a future date on the basis of study of a greater number of patients, but we wish to emphasize that our observations thus far do not confirm the belief that treatment with penicillin during pregnancy predisposes women to abortion, miscarriage or premature delivery.

The results for the Chicago group are in perfect agreement with the results for the Philadelphia and Baltimore groups. When the results for the three groups are summarized, there is a total of 96 infants in 1 of whom congenital syphilis developed and 1 of whom was stillborn. This is an over-all incidence of failure to prevent prenatal syphilis of 2.1 per cent. From the reports in the literature, Goodwin and Moore<sup>1b</sup> calculated an incidence of congenital syphilis of 15 per cent after intensive arsenotherapy. The accompanying tables indicate the correctness of Goodwin and Moore's statement, "Penicillin is incomparably superior to metal chemotherapy, no matter how administered, in the prevention of prenatal syphilis."

The contrast between the effects of intensive arsenotherapy and treatment with penicillin in preventing prenatal syphilis is also shown by the results that were obtained with the two Chicago groups of patients. While the number of patients in each group is smaller, the patients who were treated with penicillin and the patients who had intensive arsenotherapy are strictly comparable as to diagnosis and racial and socioeconomic origin.

In the preceding tables, the 59 infants who were considered to be free of infection were followed up for at least two months, and the majority were followed up for longer periods up to a year.

At the time antisyphilitic therapy was started the majority of patients in both groups were pregnant from sixteen to thirty-two weeks. The details are shown in table 4.

The favorable results of treatment with penicillin during pregnancy in preventing prenatal syphilis are surprising in view of the fact that the incidence of relapses in the penicillin-treated mothers is by no means negligible.<sup>4</sup> In the Philadelphia and Baltimore groups it was observed that normal infants, free of any signs of congenital syphilis, were born of mothers who relapsed after treatment with penicillin. One mother of the Philadelphia group had a clinical relapse (spirochetes were observed

4. The Treatment of Early Syphilis with Penicillin, Committee on Medical Research and the United States Public Health Service, J.A.M.A. 131:265 (May 25) 1946.

These differences were noted using relatively large doses (1.6 mg.) of liquid lewisite in tests on rabbits and using much smaller doses of lewisite on the human skin. No data are available on protection afforded against larger doses of liquid lewisite on human skin.

Despite the theoretic and scientific interest attached to this finding of the almost decisive roles of the vehicles in determining degree and duration of protection against lewisite, the information obtained was not of influence in selecting ointments for military issue.

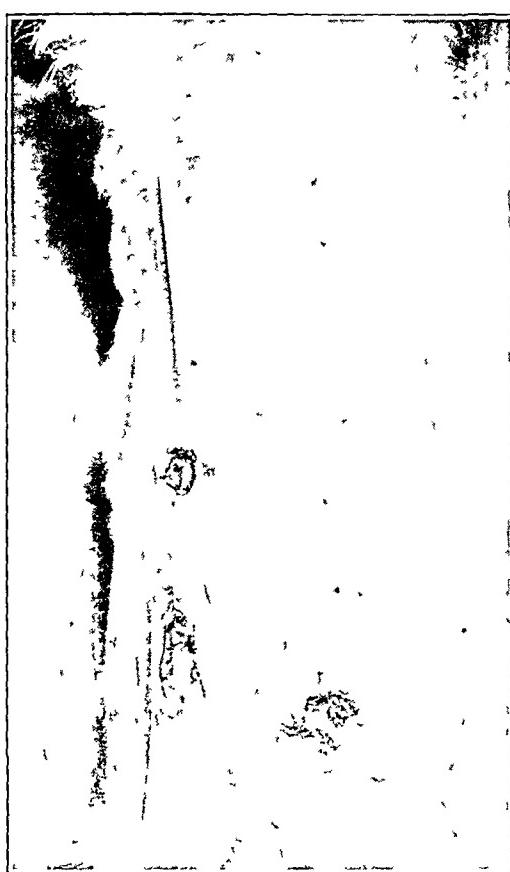


Fig. 4.—Protective experiment. Photograph three weeks after application of approximately 1.6 mg. of liquid lewisite to each of four sites. One hour preceding application of the vesicant the site at the upper right to the photograph received protective application of 10 per cent BAL in KY Jelly; lower right, 10 per cent BAL in penetrasol N; upper left, 10 per cent BAL in aquaphor; lower left, 10 per cent BAL in petrolatum. Note the great influence of the vehicle, in particular the excellent protection with KY Jelly and the poor result with petrolatum.

Among the reasons for not considering the relative protective efficacy of BAL ointments was the fact that the ointments already issued by the armed forces as protectives against mustard gas were equally effective in protecting against lewisite and other arsenicals. The BAL

CASE 2.—A 19 year old pregnant Negro girl with secondary syphilis (dark field examination revealed spirochetes) was treated with 2,400,000 units of penicillin over a period of fifteen days, sixteen to fourteen weeks before delivery (Oct. 19 to Nov. 3, 1945). On Jan. 10, 1946, she delivered a full term, apparently normal, male infant, weighing 5 pounds 13 $\frac{3}{4}$  ounces (2,658 Gm.). The infant's serologic reactions were negative at the ages of 6 weeks and 4 $\frac{1}{2}$  months. A roentgenogram of the long bones did not show evidence of syphilis. At the age of 6 weeks the infant had a faint atypical eruption on the trunk and the extremities, leaving some slightly hyperpigmented spots at the age of 8 weeks. Otherwise, the physical examination of the infant did not reveal any abnormalities at the ages of 6 weeks, 8 weeks and 4 $\frac{1}{2}$  months.

The mother, who had had quantitative Kahn reactions of 40 and 20 units, respectively, on admission, was reported as having a positive Kahn reaction one week after delivery. Five weeks after delivery this mother had relapsing secondary syphilis, confirmed by dark field examination. The Kahn titer had risen to 80 units. She was retreated with 4,000,000 units of penicillin over a period of eight days. A comparison of the Kahn reactions of the mother and the infant after delivery is noteworthy.

After Delivery	Mother	Infant
5 weeks.....	80 (relapse)	—
6 weeks.....	—	0
7 $\frac{1}{2}$ weeks.....	80	—
4th to 5th month.....	20	0

These observations and similar ones which were made in the Philadelphia and Baltimore groups indicate that treatment with penicillin during pregnancy may prevent prenatal syphilis, even though the mother is not cured and subsequently relapses with lesions showing spirochetes on dark field examination. It has been shown recently<sup>5</sup> that penicillin which is given to pregnant women passes to the fetus in relatively large quantities as early as the tenth week of gestation.<sup>6</sup> Apparently, the amount of penicillin which is transmitted from the mother to the fetus may be sufficiently great to protect or possibly cure the fetus, even though the amount of penicillin that is circulating in the mother's blood fails to eradicate the maternal infection.

This is a progress report giving the most important observations which have been made thus far. Many details will be discussed at a later date when a greater number of patients will have been treated and the infants observed for a longer period of time.

#### SUMMARY

In a group of 35 infants that were delivered of women who were treated with penicillin for early infectious syphilis during pregnancy, congenital syphilis did not develop in any infant. One infant was still-

5. Hutter, A. M., and Parks, J.: The Transmission of Penicillin Through the Placenta: A Preliminary Report, Am. J. Obst. & Gynec. **49**:663 (May) 1945.

6. Wolitz, J. H. E., and Wiley, M. M.: The Transmission of Penicillin to the Preivable Fetus, J.A.M.A. **131**:969 (July 20) 1946.

ointments were therefore not required for protection, but only for the treatment of the eye and skin exposed to arsenical gases.

#### SUMMARY

1. Experimental technics are presented for studying BAL-containing preparations applied to the skin of rabbits and men for their comparative effectiveness in decontamination, treatment and protection against damage by lewisite and other arsenical vesicants.

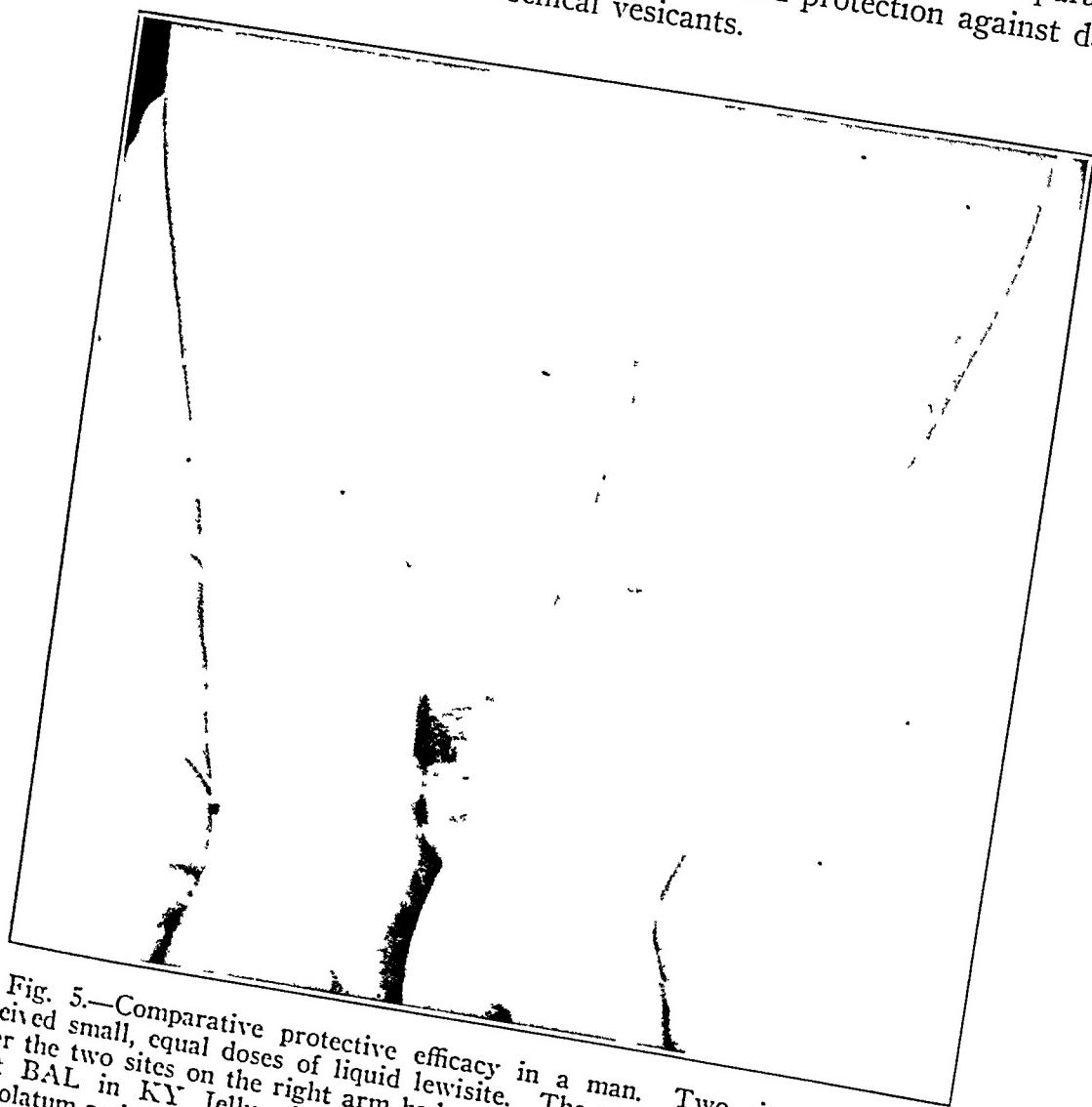


Fig. 5.—Comparative protective efficacy in a man. Two sites on each arm received small, equal doses of liquid lewisite. The vesicant was applied one hour after the two sites on the right arm had received a protective application of 10 per cent BAL in KY Jelly, the proximal site of left arm, 10 per cent BAL in petrodatum and the distal site of left arm, KY Jelly alone. Note the great influence of the vehicle, BAL in KY Jelly giving practically complete protection of both sites on the right arm and BAL in petrodatum giving poor protection to the proximal site on the left arm (photo at three days).

2. When a 5 per cent concentration of BAL was employed, the vehicle in which the BAL was incorporated did not appear to exert a great influence on the decontaminating and therapeutic efficacy of BAL.

## CUTANEOUS DIPHTHERIA

Report of Ten Cases

JOHN M. CHURCH, M.D.\*

FORT WORTH, TEXAS

AND

PERCY MASON, M.D.\*

NEW YORK

PERUSAL of the domestic and foreign literature indicates that the apparent increase of cutaneous diphtheria during and after the recent conflict closely parallels the trend observed in World War I.<sup>1</sup> While the disease is rather unusual among civilians, it occurs with some frequency among armed forces. The majority of reports deal with tropical and subtropical occurrence. With the return of large numbers of troops from areas where diphtheria is much commoner than in the United States, the possibility of cutaneous lesions should be kept in mind.

During a recent epidemic of diphtheria among American troops in Germany, 10 patients with cutaneous diphtheria were observed and treated. It is believed that their cases are of interest because of diagnostic difficulties due to the great variety of lesions and their location.

### REPORT OF CASES

CASE 1.—G. J. P., a man aged 20, was hospitalized elsewhere on Dec. 7, 1945 with a history of "athlete's foot" of three weeks' duration. On December 15 he was transferred to the Ninety-Seventh General Hospital. Bilateral dermatophytosis was present. There was a large fissure between the third and fourth toes of the right foot, extending approximately 0.5 cm. over the dorsum of the foot. A purulent exudate covered this lesion. On December 17 a "dirty membrane" over the fissure was observed. A culture was taken at this time and reported positive for *Corynebacterium diphtheriae* on December 20, whereupon 100,000 units of diphtheria antitoxin was administered. Penicillin was administered intramuscularly during the next five days. Cultures from the lesion on December 20, 21 and 24 and Jan. 12, 1946 were reported positive for *C. diphtheriae*. The membrane disappeared within seventy-two hours after the administration of the antitoxin, revealing the presence of a deep ulcer. The lesion presented an undermined edge and a clean base of a vivid red color and was not particularly painful. The

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1. Saffron, M. H.: Cutaneous Diphtheria as a Military Problem, Arch. Dermat. & Syph. 51:337 (May) 1945.

3. When a 5 per cent concentration of BAL was employed, the vehicle in which BAL was incorporated exerted a great influence on the protective efficacy of BAL.

4. The employment of proper experimental technics for biologic, chemical and physical evaluation permitted the formulation and development of relatively stable and effective BAL preparations.

5. The two best BAL preparations, one a grease base (formula A previously listed) and the other a carbowax base (formula B previously listed), developed under a program which coordinated physical, chemical and biologic evaluation of BAL in many different vehicles, were selected by the American armed forces for issue to military personnel.

with sharp edges and a purulent base 0.5 cm. in diameter. On December 24 a culture from this lesion was reported as positive for *C. diphtheriae*. The patient was immediately given 1000,000 units of diphtheria antitoxin. He was also given sulfadiazine by mouth. The lesion healed slowly. A culture of the throat on Jan. 15, 1946 was positive for *C. diphtheriae*, but subsequent cultures failed to disclose the presence of the organism. Electrocardiographic tracings were normal. The patient was discharged to duty on January 31 after forty-nine days of hospitalization.

CASE 4.—A. L. L., a white man aged 27, was admitted on Dec. 15, 1945 because of acute severe dermatophytosis of both feet. Over the dorsum of the

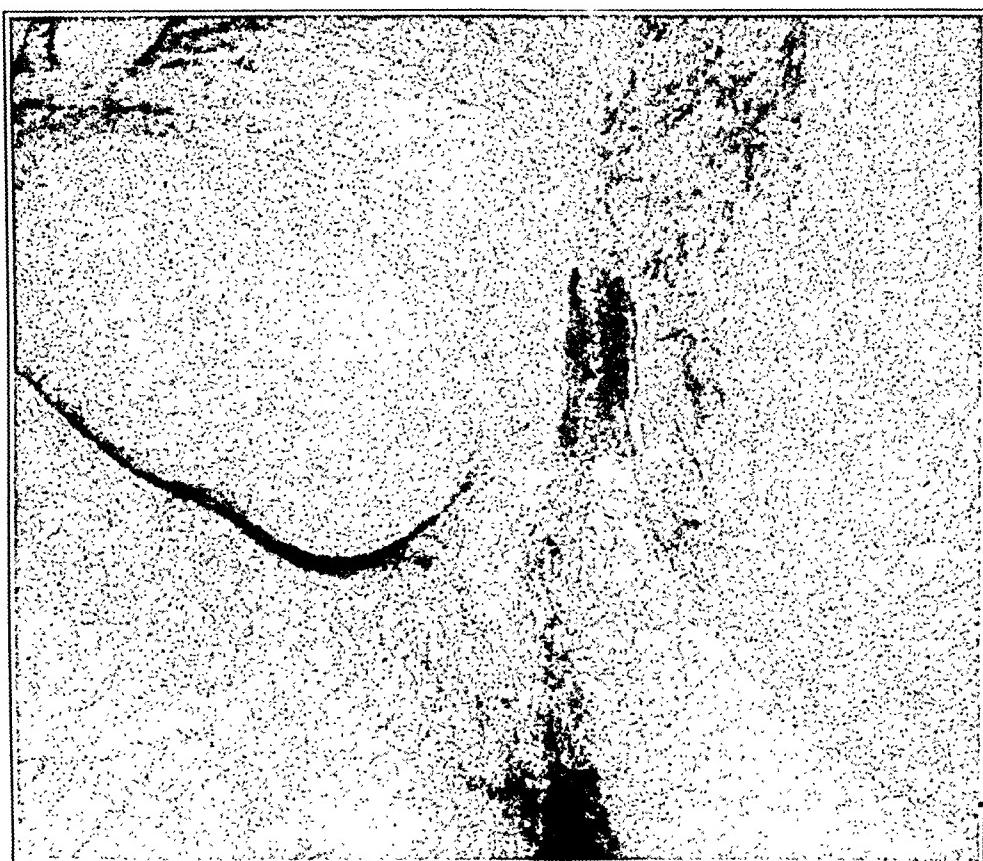


Fig. 2 (case 5).—Cutaneous diphtheria of the left genito-crural area (approximate duration, seven weeks; diphtheria antitoxin administered four weeks previously).

right foot at the base of the second and third toes was an ulcer with undermined edges of a dirty necrotic base. There was little improvement after bed rest and soaking the feet in solution of potassium permanganate. On December 31 a culture was positive for *C. diphtheriae* (reaction to the virulence test was positive), and the patient received 100,000 units of diphtheria antitoxin. The purulent discharge disappeared rapidly, and on Jan. 3, 1946 a clean ulcer with undermined edges, 1 by 0.5 cm., could be seen in the aforementioned area. The lesion healed slowly. Nose and throat cultures were consistently negative for *C. diphtheriae*. Serial electrocardiographic tracings were normal. The patient was discharged to duty on February 5 after fifty-two days of hospitalization.

## Obituaries

### ISAAC ROSENBAUM PELS, M.D. 1881-1947

Isaac Rosenbaum Pels died suddenly in Baltimore on Feb. 4, 1947, while in a barber chair, of cardiovascular disease. There had been some intimation that he had not been well for the past two years, and a few months prior to his death he had lost the sight of one eye, apparently from some vascular accident.

He was born in Baltimore on Oct. 8, 1881, the son of Moses and Helen Rosenbaum Pels. He attended public and private local schools and received his degree of Bachelor of Arts from Johns Hopkins University in 1902, and his degree of Doctor of Medicine in 1906. He served an internship at the Union Memorial Hospital and then took postgraduate work in dermatology in Europe in 1909 and 1910.

He married Margaret Riggs Black on Aug. 26, 1926. They have one daughter, H. Patricia Pels, and a son, John Marshall Pels.

On his return from Europe Dr. Pels began the practice of dermatology in Baltimore, which was uninterrupted except for two years which he spent at Saranac Lake for a tuberculous infection. He had been associated with the Department of Dermatology at the Johns Hopkins University since he began the practice of medicine, and at the time of his death he was assistant professor. He was also dispensary dermatologist to the Johns Hopkins Hospital, attending dermatologist to the Church Home and Union Memorial Hospital, Sinai Hospital and the City Hospital, consultant in dermatology at Sydenham Hospital and the Baltimore Eye, Ear, Nose and Throat Hospital. He was associated with the late Dr. J. Williams Lord for many years in the practice of dermatology but established his own office in 1925.

He was a member of the Medical and Chirurgical Faculty of Maryland, the Baltimore City Medical Society, the Baltimore-Washington Dermatological Society, the Maryland Academy of Sciences and the American Dermatological Association.

In his younger days he was fond of fishing and golf and was always interested in the theater and in music.

He was intensely devoted to his own specialty, both its practical side and historical aspects. He had some fine old editions and at one

on this date and continued for five days. The ulcer filled in slowly, and the edema disappeared. Electrocardiographic tracings revealed the T waves to be somewhat flat initially, regaining normal amplitude one month later. Nose and throat cultures were consistently negative for *C. diphtheriae*. The patient was discharged to duty on March 3 after seventy-six days of hospitalization.

CASE 7.—G. A. M., a white man aged 37, was hospitalized on Jan. 12, 1946 with a history of having been treated for dermatophytosis of the hands and feet

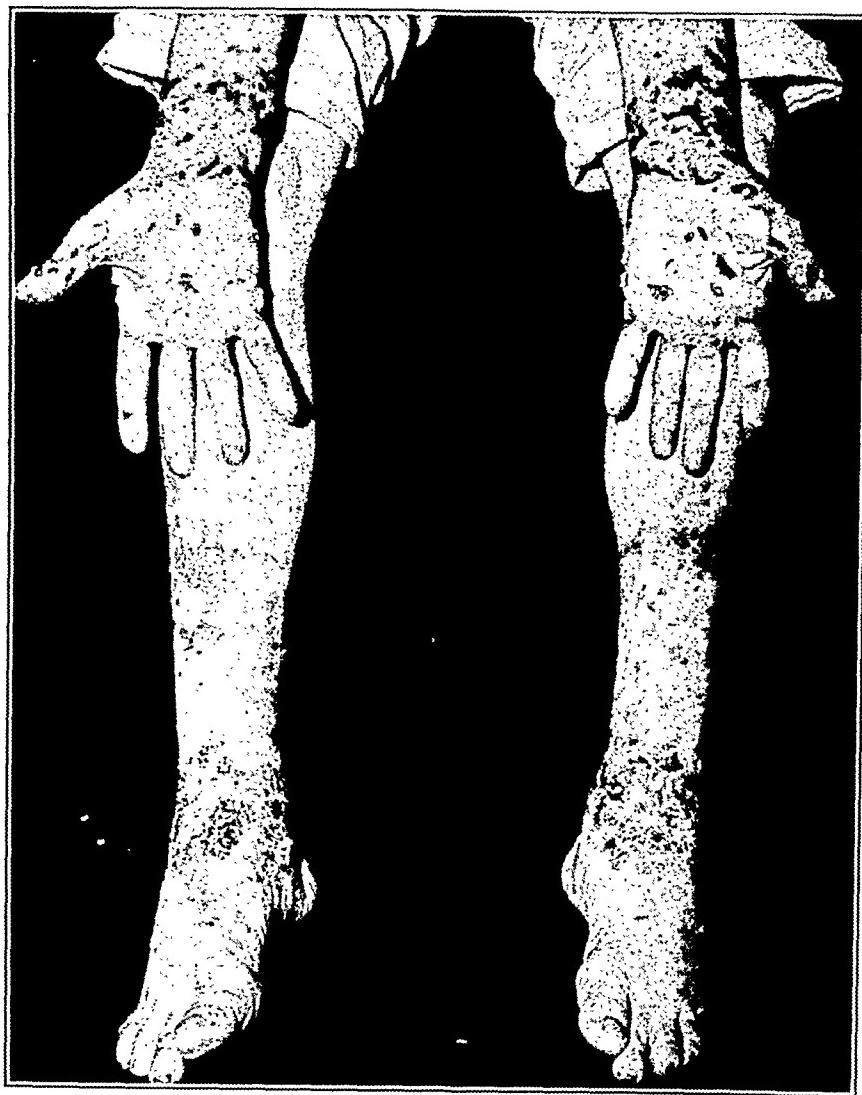


Fig. 4 (case 7).—Cutaneous diphtheria of the legs, hands and wrists (approximate duration, three months; picture taken immediately prior to the administration of diphtheria antitoxin).

since October 1945. In the twelve days prior to admission the eruption had become considerably aggravated. The lower half of both legs presented decided impetiginous lesions. The hands presented extensive exfoliation, especially of both palms, with impetiginous lesions on both wrists (fig. 4). Improvement was not noted after local application of solution of aluminum acetate, N. F. Cultures from the lesions of the hands were positive for *C. diphtheriae* on January 26 and 28. One hundred thousand units of diphtheria antitoxin was administered on

time organized a Journal Club, where he and his colleagues met and discussed various phases of dermatologic literature, both past and present. He attended faithfully the local medical meetings and was always much interested in trying to stimulate the young men to take part in such meetings by a free discussion of the cases.



ISAAC ROSENBAUM PELS, M.D

1881-1947

He made a number of contributions to dermatologic literature, the most notable contribution being one dealing with the Pels-Macht phytopharmacologic test, which has been of value in the diagnosis of pemphigus.

Dr. Pels was a very kind man and deeply concerned in the welfare of his patients, all of whom loved him. He will be missed by the medical profession as well as by the citizens of Baltimore.

L. W. KETRON, M.D.

healed slowly, leaving small atrophic scars. Serial electrocardiographic tracings revealed a decided depression of the QRS complex and the T wave in all leads. Considerable improvement occurred after five weeks of absolute bed rest.

#### SUMMARY

Ten cases of cutaneous diphtheria are reported. The lesions presented a diversified appearance and occurred on the extremities, the lower part of the abdomen and the genitalia. Diphtheria antitoxin was administered intramuscularly to all patients. In addition, some of the patients received nonspecific chemotherapy (penicillin, sulfadiazine and thiamine hydrochloride). Local nonspecific therapy was also employed. All patients required lengthy hospitalization. Electrocardiographic evidence of myocardial damage and peripheral neuritis was encountered. Throat cultures were positive for *Corynebacterium diphtheriae* in 3 cases.

1212 West Lancaster Avenue, Fort Worth.

HARRY LOUIS CLAASSEN, M.D.

1892-1947

Harry Louis Claassen died at the height of his successful career on Jan. 11, 1947, at the age of 54, while professor of dermatology and syphilology at the University of Cincinnati College of Medicine.



HARRY LOUIS CLAASSEN, M.D.

1892-1947

In August 1925 he married Mary Longwith, whose loyalty, devotion and companionship were sources of great comfort and stimulation in his professional and private life.

In Army Air Forces personnel the type, incidence and importance of cutaneous diseases vary according to the assignment of the soldier. The causes of contact dermatitis of a gunner will differ from those of the disease in a pilot. A thorough knowledge of their duties and of the substances they handle is a great asset in the proper management of dermatologic cases. This refers not only to dermatitis venenata but to other cutaneous diseases as well.

Other factors which may possibly play a role in cutaneous diseases in air force personnel are physiologic changes occurring at high altitude, such as aeroembolism, and sudden extreme changes of temperature. Little is known of the importance of these factors, since practically no research has been made on these problems from the dermatologic standpoint. The expected greater development of aviation in the postwar period makes this an interesting new field for research.

This paper is intended to summarize the experience gained by me in two years as chief of the dermatologic sections at two large air bases in the Southwest, one of them a regional hospital. These bases were engaged in training combat crews for heavy bombers. The dermatologic section consisted mainly of a large outpatient clinic. Patients requiring hospitalization were treated in the ward. In this paper a discussion will be made successively of the present knowledge of the physiologic changes of the skin in flight, the incidence of cutaneous diseases at the dermatologic clinic and the diseases of special importance in air force personnel.

#### PHYSIOLOGIC EFFECTS OF FLYING ON THE SKIN

In spite of the great and rapid advances of aviation medicine, little has been written on the physiologic effects of flight on normal and pathologic skin. Only occasional references to cutaneous changes are found in the literature. Most of these notes are brief, since they have been made during the study of other organs.

From the standpoint of cutaneous diseases, the most important changes encountered in flight are the variations of barometric pressure and the sudden changes of temperature. One of the main effects of changes in pressure on the human body is aeroembolism (decompression sickness and bends). This is characterized by the formation of nitrogen bubbles in the body tissues and fluids. It is due to the fact that in rapid ascent to high altitudes the amount of dissolved nitrogen in the body is in excess of that which can be held in solution. When the ascent is rapid to altitudes of 30,000 feet or more, the nitrogen gas will tend to come out of solution and form bubbles not only in the blood but in other tissues as well. Different factors are important in the production of aeroembolism, such as the rate of ascent, altitude attained, time the person

He was a devoted and worthy servant to his profession, with a sympathetic understanding of the poor and unfortunate, to whom he gave much of his life. Always a person of temperate habits and modest requirements, Dr. Claassen's death was hastened by his loyalty and devotion to others. His final illness came while he was treating a patient in his office

skin repeatedly exposed to such conditions. Burrill and colleagues<sup>4</sup> showed that exposure to 18,000 feet (5,486 meters) caused a temporary rise in the excretion of sodium, potassium and chlorides.

Undoubtedly the skin plays a role in this process, since it is one of the greatest reservoirs of chloride. The possible changes of the blood cholesterol at low barometric pressure were investigated by Muller and Talbott,<sup>5</sup> with negative results. However, Schemenky<sup>6</sup> found increased values following exposure to high altitude. The importance that this fact may have in dyslipidosis remains to be determined.

With the purpose of ascertaining the effect of flying on different cutaneous diseases, patients on flying status were always questioned about the effect of flying on the condition of their skin. This, although wholly inadequate to make definite statements, gives a hint on the reaction of cutaneous diseases to flying conditions. The result obtained by such inquiry showed that most diseases of the skin are not appreciably affected by flying at high altitude. Occasionally pruritus was exacerbated. This was frequently the case in pruritus ani, pomphyolyx, dermatophytids and similar eruptions. It is impossible to determine to what extent the nervous tension associated with flying or the sudden changes of temperature may have had in the appearance or aggravation of pruritus.

In summary it can be said that there is surprisingly little information on the physiopathologic changes of the skin exposed repeatedly to flying at high altitude. There is a great need for research to clarify many obscure points on this subject. These studies should be made by qualified personnel, it being kept in mind that the skin is an important functioning organ and not merely a passive membrane structure.

#### STATISTICAL DATA

The dermatologic clinic was operated as part of the medical service. The data here given include material from two stations—one, a station hospital, in which the skin clinic was operated for nine months, and the other, a regional hospital, where the clinic functioned for thirteen months. The clinic of the latter was larger, averaging 16 military patients daily. The total number of patients seen was 2,327. The total number of visits per patient was 4.2. With the purpose of decreasing the noneffectiveness of cutaneous diseases and preventing the interruptions of training as much as possible, hospitalization was kept to a minimum. At the

4. Burrill, M. W.; Freeman, S., and Ivy, A. C.: Sodium, Potassium and Chloride Excretion of Human Subjects Exposed to Simulated Altitude of Eighteen Thousand Feet, *J. Biol. Chem.* **157**:297 (Jan.) 1945.

5. Muller, G. L., and Talbott, J. H.: The Effect of High Altitudes on Cholesterol, Lecithin and Fatty Acids in the Plasma of Healthy Men, *Arch. Int. Med.* **47**:855 (June) 1931.

6. Schemenky, cited by Muller and Talbott.<sup>5</sup>

titis produced by substances such as fluids, greases and solvents, with which personnel come in contact in the process of repair, maintenance and operation of airplanes and (b) dermatitis venenata produced by equipment or clothing used by flying personnel.

Dermatitis Venenata Produced by Substances Handled in the Repair, Maintenance and Operation of Aircrafts: This is most frequently encountered in ground crews, although it may be present in members of the flying personnel engaged in mechanical work, as engineers, or those handling irritants used in cleaning of their equipment, such as gunners. Civilians working in repair depots are subject to similar hazards. Fletcher Hall<sup>7</sup> found that zinc chromate is, by large, the commonest cause of dermatitis venenata in the aircraft industry. He demonstrated that the terms "dural poisoning" or "aluminum poisoning," commonly used by workers and physicians, are incorrect, since in only 5 per cent of his cases were the conditions found to be due to dural and in only 2 per cent to aluminum. In 65 per cent zinc chromate was responsible for the dermatitis.

A good knowledge of the chemical nature of the substances used by the personnel engaged in repair and maintenance of airplanes is essential for the proper management of patients with dermatitis venenata. For instance, a gunner in his routine work handles a certain number of lubricating oils and cleaners which differ from those used by engineers or ground crew mechanics.

Armstrong<sup>8</sup> classified the primary irritants encountered in the repair and maintenance of aircrafts into six groups: (1) dopes, paints and related materials; (2) cleaning materials; (3) fire-extinguishing compounds; (4) engine exhaust gases; (5) aviation gasoline, and (6) hot oil fumes. Only some of those are important from the dermatologic standpoint. A complete list of the potentially irritating substances handled by ground crews and flying personnel is not within the scope of this article. Only the most important ones will be discussed here. Among the substances handled by air force personnel which are known to be irritants to the skin are (1) carbon tetrachloride (used as cleaning fluid to clean parts of engines, propellers, radar, bombsights, parachute harnesses and other materials; it is also used as a fire extinguisher); (2) ethylene dichloride (used for removal of carbon, as fuel cell repair and as paint remover); (3) trichloroethylene (used as a degreaser); (4) benzine (also used as a degreaser); (5) toluene (employed as thinner, dope and degreaser), and (6) aviation gasoline. The last is a complex fluid containing tetraethyl lead and xylidin.

7. Hall, A. F.: Occupational Contact Dermatitis Among Aircraft Workers, J. A. M. A. 125:179 (May 20) 1944.

8. Armstrong,<sup>2</sup> p. 166.

The maceration of the warty tissue with the salicylic acid and the paring away of the surface should have promoted absorption of the resin of podophyllum with the aid of the penetrant vehicle.

It has been suggested that condyloma acuminatum and verruca vulgaris are caused by the same filtrable virus. Serra<sup>6</sup> produced warts on the skin with Chamberland filtrate of condyloma acuminatum and Findlay<sup>7</sup> with Berkefeld-filtered material. The failure of verruca vulgaris to respond to the same chemical therapy as did condyloma acuminatum makes questionable the thesis that these two entities have a common cause.

#### SUMMARY

Resin of podophyllum incorporated in a penetrant vehicle as a treatment for verruca vulgaris has been observed to be unsuccessful, even when the horny layer is first macerated by chemical action or removed by surgical procedures. This observation suggests that verruca vulgaris may not be caused by the agent which causes condyloma acuminatum, which responds so readily to therapy with resin of podophyllum.

Medical Center, White Plains, N. Y.

1007 Greenwood Avenue, Trenton, N. J.

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5. Sulzberger, M. B., and Wolf, J.: The Treatment of Warts by Suggestion, M. Rec. 140:552 (Nov. 21) 1934.

6. Serra, A.: Studi sul virus della verruca, del papilloma, del condiloma acuminato (etiology, patogenesi, filtrabilità), Gior. ital. d. mal. ven. 65:1808 (Dec.) 1924.

7. Findlay, G. M.: Warts, in A System of Bacteriology, London, His Majesty's Stationery Office, 1930, vol. 7, p. 253.

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#### TRANSITORY BENIGN PLAQUES OF THE TONGUE

##### Treatment with Penicillin

CLARENCE SHAW, M.D., CHATTANOOGA, TENN.

Two patients with transitory benign plaques of the tongue have been benefited by the local use of a solution of penicillin.

#### REPORT OF CASES

CASE 1.—M. K., a 22 year old white nurse, was seen with an eruption on the tongue of over three years' duration. The lesions came and went in rapid succession and were practically asymptomatic. Treatment in the past had included two roentgen ray treatments of 75 r each, which had cleared the tongue for eight to ten days, after which the disorder recurred.

Examination showed discrete and confluent round slick pink patches with gray borders on the sides and dorsum of the tongue. Oral and dental hygiene was good. Bacteriologic studies showed the presence of a staphylococcus (facultative aerobe) and an anaerobic nonhemolytic streptococcus.

She was given a solution containing 1,000 units of calcium penicillin per cubic centimeter of isotonic solution of sodium chloride to use as a mouth wash three times a day. The next day the eruption was improved, and within four days there

masks and throat microphones are an important source of irritation on chin, neck and about the mouth. The warm dry climate of the geographic area where this study was made seems to have beneficial effect on acne by decreasing the activity of the sebaceous glands and thus reducing the oiliness of the skin. However, on many occasions, severe eruptions with cystic lesions were encountered, making flying personnel unfit for duty.

*Dermatophytosis.*—Fungous infection of the feet was commonly seen, especially in summer. The mild intertriginous form was the type most frequently observed. Since the type of activities of air force personnel does not require too strenuous exercises or long marches, hospitalization was successfully kept at a minimum and reserved for severe conditions complicated by secondary infection.

*Tinea Cruris.*—Tinea cruris was rather common in flying personnel. It was often aggravated by friction of the lower straps of the parachute harness. Grounding a patient for a few days was found to be a great help to the local treatment.

*Verruca Plantaris.*—Verruca plantaris was observed only rarely. Its incapacitating nature is minimal, except possibly in some pilots. In them the disease may handicap the steady pressure on pedals required for the control of some types of planes.

*Miscellaneous Diseases.*—Pruritus ani was rather frequently the cause of disability. The nervous tension associated with flying, together with the long hours sitting required on long missions, made this disease a major problem in some cases. Dermatophytids, dyshidrosis and hyperhidrosis may be a handicap in combat crews, as they may hamper the efficiency of a bombardier or a gunner at the precise moment when it is most needed. Here too, the nervous tension of flying or combat may play an aggravating role. Painful nodules of the ear were occasionally seen. The mechanical irritation of earphones may have contributed to their formation.

#### SUMMARY AND CONCLUSIONS

1. Dermatologic problems encountered in Army Air Forces personnel are discussed. The study covers a period of two years and was made at the skin clinic of two large air bases in the Southwest, one of them a regional hospital. A total of 2,327 patients was seen.
2. The ten diseases of the skin most commonly seen are presented. The first three were dermatitis venenata, pyogenic infections and fungous infections.
3. The diseases of special significance to air force personnel are discussed. The importance of dermatitis venenata is stressed. It may be produced by substances, materials or equipment handled during the

injections. The patients usually complained of numbness and stiffness of the leg immediately or at any time up to thirty minutes after the injection. Many of the patients required assistance in order to leave the office after the injection because of what they described as a "paralysis" of the leg. This often lasted for several hours. Soreness might persist for days. There was no formation of nodules.

Despite the usual precautions in aspiration, apparently a small amount of the concentrated solution entered the blood stream in 1 patient (case 14). This resulted in symptoms of shock. The patient became weak and cold. The pulse was imperceptible, and hypotension developed. A feeling of impending death ensued. The patient was not sufficiently recovered to leave the office for an hour.

Several patients complained of nausea after the injection. One insisted that she started to menstruate within fifteen minutes after each of the six injections that she received (case 13). No pregnant women were treated with this agent.

#### COMMENT

Aminophylline, injected intravenously or intramuscularly, is an effective antipruritic agent. However, its toxicity and the short duration of its effect make one hesitate to use it intravenously. The high frequency of reactions prevents its full use intramuscularly. Four patients, all of whom had been undergoing treatment for some time, failed to return after one or more painful reactions to injections of aminophylline.

From this report it can be seen that the methods thus far suggested are impractical for the routine use of aminophylline as an antipruritic agent.

Some work has been done on administering the dose of 0.5 Gm. of aminophylline in 1,000 cc. of solution of dextrose or isotonic solution of sodium chloride. The therapeutic results have not been satisfactory, but the toxicity, both immediate and delayed, has apparently been eliminated. It is possible that the dose of aminophylline could be given intravenously in 100 to 500 cc. of solution with safety and efficacy.

#### SUMMARY

Seventeen patients with various severe itching dermatoses were treated with the intramuscular injection of 0.5 Gm. of aminophylline in 2 cc. of solution. In 7 patients the relief of itching was dramatic. However, the local and general reactions were so severe as to prevent the general use of this drug as an antipruritic agent.

The material used in this study was furnished by G. D. Searle & Co.

week and then one shampoo each third day for at least two more weeks. Although I have no figures to quote, it is my impression that the sulfur foam cloths are valuable when used in conjunction with other local therapy.

The use of the sulfur foam cloth makes possible the application of sulfur throughout the scalp in a convenient manner and permits treatment to the minute foci of infection which probably have escaped detection by examining physicians.

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#### RAPID METHOD FOR SEEDING NAIL CULTURES

ABNER KURTIN, M.D., and REUBEN YONTEF, M.D., NEW YORK

The technic of nail culture to demonstrate fungous infection, in our experience, has not been satisfactory. Scrapings of suspect nails may be difficult to secure, and the tiny particles which are teased away present manipulative difficulties when they are transferred to the culture medium.

As a step in the therapeutic management of infected finger nails, as originally suggested to us by Dr. Samuel Peck, it has been our custom to employ an electric hand drill which quickly and painlessly pares away diseased nail substance.



Seeding a nail culture with an electric hand drill

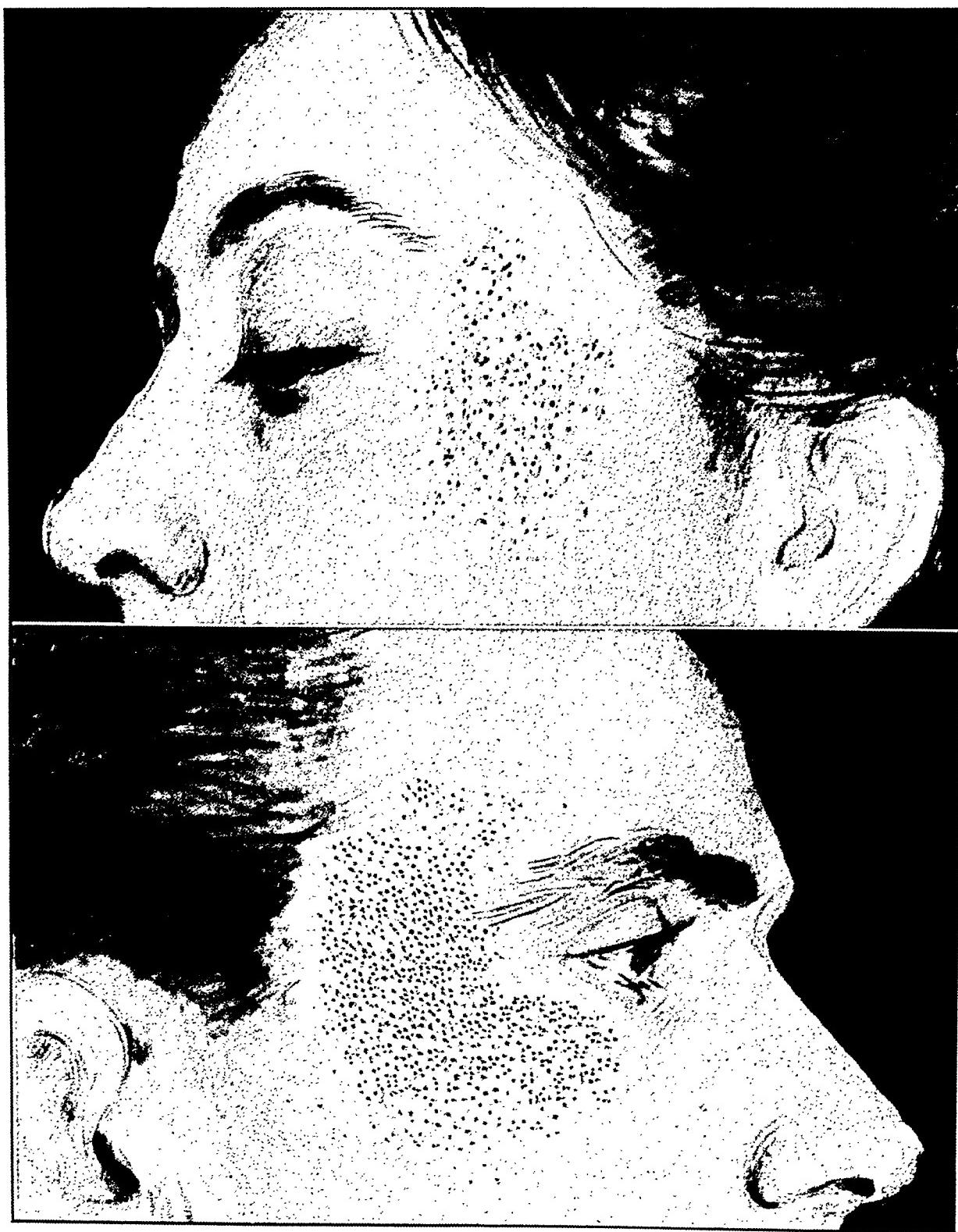
Whenever the rapidly revolving burr makes contact with the nail a fine cloud of nail dust is thrown forward in the direction of revolution.

It occurred to us that if this particulate stream were to be directed into a culture medium, it would afford a rapid and effective method for thoroughly seeding a slant culture or a Petri dish. Experience has confirmed the value of this method. Its rapidity decreases the possibility of surface contamination.

The accompanying photograph illustrates the simplicity of the technic.

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From the Dermatological Service of Mount Sinai Hospital.



Comedos localized in the temporozygomatic area.

## OTORHINOPHYMA, PRURITUS AND ALOPECIA TOTALIS SYNDROME

Response to Testosterone

SAMUEL AYRES Jr., M.D.  
AND  
ANKER K. JENSEN, M.D.  
LOS ANGELES

THE PATIENT herein described presents a clinical picture which is unlike anything encountered in our experience and which, so far as we can determine, has not been described in available medical literature. At the time the patient was presented before the Los Angeles Dermatological Society over two years ago<sup>1</sup> no one who saw him had ever observed a similar case, and the majority of the physicians who discussed the case felt that it represented either some type of lymphoblastoma or some unusual clinical entity. After publication of this report, Dr. Norman Tobias, of St. Louis, in a personal communication,<sup>2</sup> expressed his interest in the case and stated that he had recently seen a patient who, he felt, presented an identical picture. More recently, Dr. Tobias, in reply to a brief questionnaire, indicated that his patient not only exhibited the same clinical characteristics but also responded in a similar manner to treatment.

While it is obviously imprudent to draw conclusions from a single case or, at best, from 2 cases, and while the good results of treatment obtained in these 2 cases might not be duplicated, yet the objective appearance and discomfort of our patient were so extraordinary and the therapeutic results were so dramatic that it seemed worth while to record the case in detail.

### REPORT OF A CASE

A. R. L., an American-born white man aged 66, entered the Los Angeles County General Hospital on the dermatologic service Oct. 1, 1943 because of changes in the skin. The onset of the changes was about fifteen years before, when the patient

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From the Department of Dermatology and Syphilology of the Los Angeles County General Hospital.

Read at the Sixty-Sixth Annual Meeting of the American Dermatological Association, Inc., Hot Springs, Va., June 1946.

1. Ayres, S., Jr., and Jensen, A. K.: A Case for Diagnosis (Lymphoblastoma?), Arch. Dermat. & Syph. 49:457 (June) 1944.

2. Tobias, N.: Personal communications to the authors.

Examination showed a linear distribution of yellowish, pinhead-sized nodules, extending from the inner edge of the left eyebrow to the inner part of the left lower eyelid. In the lowest part of the nevus was a pea-sized, crusted, hyperkeratotic lesion on an inflammatory base. On superficial examination this appeared to be a cutaneous horn. This lesion was removed with a curet. Biopsy showed a prickle cell epithelioma of high grade malignancy.

When the patient returned, after two weeks, the lowermost nodule had recurred and enlarged to the size of a hazelnut. At this time the entire lesion was widely and deeply removed, a second biopsy performed and intensive roentgen therapy administered.

The second biopsy revealed a squamous cell epithelioma of high grade malignancy.

#### DISCUSSION

DR. MOLLEURUS COUPERUS: What could be seen here seemed to me in the nature of a linear sebaceous nevus, and I was not able to see any clinical evidence of a prickle cell epithelioma. I did not see the section.

DR. L. H. WINER (by invitation): This is the second case I have seen in which squamous cell epithelioma developed in a nevus unilateralis. The section showed features of both basal and squamous cell carcinoma. An epithelioma developing in such a nevus is resistant to roentgen therapy. Another patient with this type of lesion had heavy irradiation, without success, and finally complete excision had to be performed.

DR. N. P. ANDERSON: The child is 8 years old, and cancer in one of that age is usually looked on as serious. Another important point in this case is the development of the epithelioma in the nevus. At first I thought it was a wart or a cutaneous horny growth; so I simply took it off with a curet and desiccated the base fairly heavily. I was surprised at the high grade of malignancy as revealed by biopsy. When the patient returned three weeks later, the recurrent lesion was as large as a hazelnut. I removed it widely and deeply. These linear nevi have been regarded as benign, but many of the patients die of cancer later in life.

#### A Case for Diagnosis (Granuloma Annulare? Lupus Erythematosus Tumidus?). Presented by DR. J. WALTER WILSON.

G. W., a white woman aged 53, of American stock, whose mother died at the age of 47 with carcinoma of the breast, gave no history of tuberculosis in herself or in her family. Two months ago a plaque appeared on her face, which was somewhat larger than the one she now presents. It underwent involution in the center until the present annular lesion resulted. The process has been symptomless except for occasional slight itching.

At the inferior border of the right nasolabial fold is a lesion 1.4 cm. in diameter, with a rolled, pearly, shiny border and a depressed, erythematous central pit. The border is firm, and the induration extends beyond the borders of the visible lesion.

Histologic examination showed that the epidermis was somewhat thinner than normal and had occasional edematous areas. The keratin layer was thin and the granular layer normal. A moderate amount of follicular plugging was present. In the dermis, the abnormalities consisted of perivascular and perifollicular round cell infiltration in the upper portion, while numerous syncytial cells, resembling giant cells, together with some fat replacement atrophy, were seen in the deeper areas.

#### DISCUSSION

DR. W. H. GOECKERMAN: The differential possibilities are fairly complete as discussed, but did not include a syphilid, a diagnosis which I favor above the others. The plaque is of the reasonably superficial type, biologically a late secondary or an early tertiary lesion; in either case destruction of tissue is minor. I should favor this diagnosis even if the Wassermann reaction of the blood were negative. A careful therapeutic test should clinch the diagnosis.

redness, scaling and excoriations of superciliary areas, nose, chin, mouth and especially the ears. The nose was bulbous and almost twice the normal size. The ears were swollen to approximately twice their normal size, and there were a number of small ulcers and oozing in the region of the concha.

The facial appearance was so grotesque as to be suggestive of a gargoyle. The oddness of the patient's appearance was heightened by the glass eye on the left side. The vision in the right eye was fair, and the pupil reacted normally to light and accommodation.

The skin elsewhere on the body was covered with small discrete maculopapules covered with crusts and excoriations and surrounded by an erythematous halo. These were most numerous on the legs with a few on the arms and trunk. The finger nails were atrophic and "warped." The heart, lungs and abdomen were normal.

*Laboratory Data.*—Hematologic studies made on Oct. 4, 1943 showed a hemoglobin level of 12.8 Gm. (80 per cent); red blood cells, 3,970,000; color index, 1.09;



Fig. 2.—Appearance nineteen months after oral administration of methyl testosterone for only four months, showing the growth of hair and subsidence of ears and nose.

white blood cells, 15,700 and reticulocytes, 0.8 per cent. The platelets were normal in number, toxic granulation was moderate, and there was slight anisocytosis. The differential count showed: neutrophils, 42 per cent; large lymphocytes, 20 per cent; small lymphocytes, 22 per cent; monocytes, 6 per cent; eosinophils, 3 per cent, and "blasts," 7 per cent. Comment by the hematologist: "This was compatible with a certain stage of Schilling type leukemia, but it is not impossible that this was a reactive blood."

Hematologic studies made on Nov. 10, 1943 showed a hemoglobin level of 12.16 Gm. (76 per cent); red blood cells, 3,560,000; color index, 1.15, and white blood cells, 21,050. The platelets appeared normal, and the red blood cells showed slight hyperchromasia. The differential count was as follows: neutrophils, 61 per cent; lymphocytes, 27 per cent; monocytes, 7 per cent, and eosinophils, 5 per cent. Comment by the hematologist: "There was no evidence of hematologic disorder, except that there was leukocytosis with absolute lymphocytosis."



Fig. 3.—Specimens from the ear, showing thickened epidermis and dilated follicles and terminating in cystlike dilatations and cellular infiltration.

DR. M. E. OBERMAYER: Although there is imminent danger of squamous cell epithelioma, I am not convinced that the malignant change has actually taken place. The patient merely presented dermatitis actinica and keratoses. Biopsy should be performed, as the absence or presence of epithelioma would determine the therapeutic course.

DR. JOHN D. ROGERS: This case serves to demonstrate the importance of the judicious use of roentgen rays. Probably the best step would be to have a biopsy of the lesion on the finger and proceed according to the microscopic observations. Otherwise, perhaps only soothing applications should be used. The disease has not responded well to local treatment; crude coal tar ointment seemed to help somewhat.

DR. J. WALTER WILSON: Radon ointment or alpha radiation applied in ointment form is beginning to have a rather good reputation for the treatment of actinic dermatitis.

**Pityriasis Versicolor, Achromic? Achromic?** Presented by DR. H. C. L. LINDSAY, Pasadena, Calif.

A young white woman, a university student, noticed that after intense and prolonged exposure to the sun on the beach formerly brownish macules on the back and chest, which she had had for some time, had become whitish.

Examination showed slightly depigmented macules, varying in size from 0.5 to 1 cm. in diameter, on the upper part of her chest and back. Scraping revealed the presence of *Malassezia furfur*.

DISCUSSION

DR. M. E. OBERMAYER: I thought that this was a typical case of pseudo-achromia parasitica, the whitish color of the lesions being caused by *M. furfur* in persons who have a sun-tanned skin. It seems to me that this disorder is becoming increasingly frequent, and I should like to know whether other members share this impression.

DR. A. F. HALL JR., Santa Monica, Calif.: I have seen this disease with more than the usual frequency of late, and not alone in persons who fail to bathe. I was taught that pityriasis versicolor occurred only in people with unclean habits. I do not agree with this assumption, as I have seen it frequently in people who are of undoubtedly cleanly habits.

DR. H. P. JACOBSON: The diagnosis in this case is obvious—pityriasis versicolor. In the tropics *M. furfur* is frequently troublesome. Instead of non-inflammatory, furfuraceous, barely elevated patches, the lesions assume inflammatory characteristics and may become disabling. The present patient shows a widely distributed form of the infection. Evidence of spread of this infection in this part of the country has been observed by many dermatologists. Whether it is being transported to the shores of this country from the South Pacific I do not know. The treatment of this infection must be thorough. The patient should scrub nightly with soap and water, followed by an application of 10 to 20 per cent sulfur ointment for five to seven nights in succession.

DR. A. K. JENSEN: The best treatment for pityriasis versicolor in my hands has been the use of a saturated solution of sodium thiosulfate following a hot bath, together with exposure to desquamating doses of ultraviolet radiation once a week.

**A Case for Diagnosis (Erythema Multiforme?).** Presented by DR. FLORALOU KETTENBACH (by invitation).

Mrs. J. G., a white woman aged 68, has had a chronically recurrent, exceedingly pruritic eruption for seven years. At first recurrences took place only in the fall. Since last March, however, they have been continuous. The lesions were usually of the type presented here and as a rule were confined to the knees and the feet. At times they were simply urticarial wheals. At other times they showed an iris configuration. On several occasions "vesicles" were present in the mouth. No scars were left. The patient had been examined by a number of dermatologists

In this section (figs. 5, 6 and 7) the epidermis showed little, if any, abnormality. One large epithelial cystlike structure occupied a conspicuous location in the upper layer of the midcutis. A dense infiltrate was present in the upper layer of the cutis and extended to the deeper portions, especially surrounding the cyst. This infiltrate was polymorphous, consisting mostly of small round cells with some plasma cells, some cells of miscellaneous type, a few polymorphonuclear neutrophils and a few eosinophils, but not so many eosinophils as in the first specimen.



Fig. 5.—Section of tissue showing large epithelial cystlike structure and dense lymphoblastoma-like infiltration.

Bacteriologic studies of scrapings and pus from paronychial areas were made on Oct. 28, 1943. A smear showed epithelial cells, a few staphylococci and gram-positive bacilli. A culture for *Staphylococcus albus* on Sabouraud's medium showed no growth.

(Clinical note: Of the two attending dermatologists who first saw the patient in the dermatologic clinic, one offered a diagnosis of possible mycosis fungoides while the other suggested alternatives of lymphoblastoma or leprosy.)

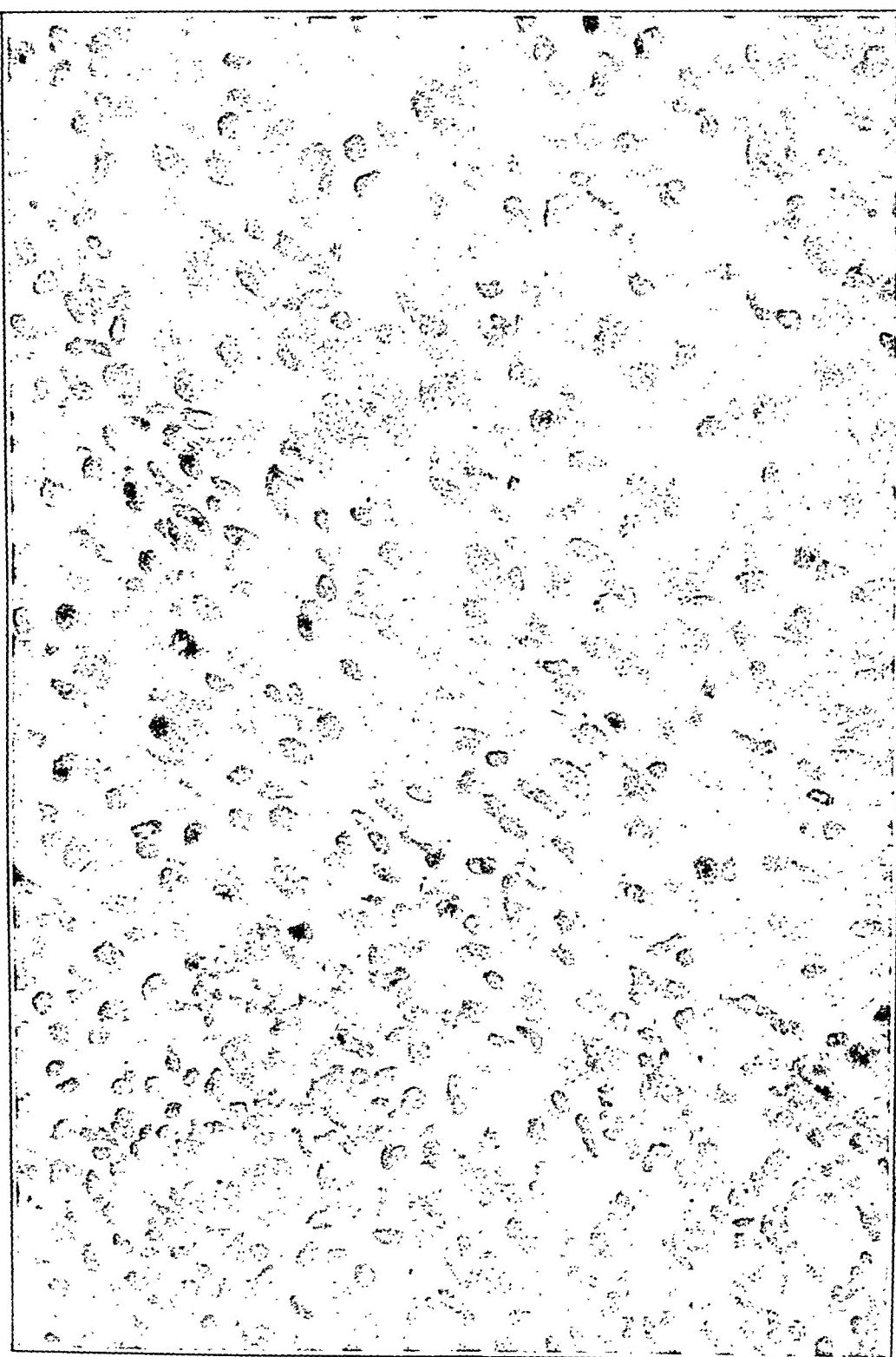


Fig. 7.—Dense polymorphous infiltrate in the cutis.

to get the idea from this article that simply because erythema multiforme is related to herpes simplex in many cases I feel it is the only etiologic agent. I have not made any virus studies. As a matter of fact, when I read various articles by authorities on virus diseases, I find a good deal of disagreement with regard to the isolation and study of viruses.

**Multiple Lipoma.** Presented by DR. SAMUEL AYRES JR.

S. M. B., an Arabian man aged 50, had noted the gradual appearance of four or five lesions on his arms and forehead over a period of twenty years. These were removed surgically about four years ago, and no more lesions occurred until four months prior to his first visit, on April 13, 1945. After a fall from a horse at that time large numbers of nodules began to develop. He gained 30 pounds (13.6 Kg.) during these four months.

A large number of nodules are scattered over the body, especially over the ulnar aspect of the forearms, over all aspects of the thighs, buttocks and legs, and to some extent elsewhere. The lesions are approximately the size of marbles or larger; they are movable and somewhat doughy, and some are slightly pink. Some of them are slightly tender.

The plasma cholesterol measured 241 mg. per hundred cubic centimeters. The dextrose tolerance test was normal.

Treatment has consisted of a low fat diet since April 1945.

DISCUSSION

DR. H. C. L. LINDSAY, Pasadena, Calif.: I presented 3 patients with multiple and painful subcutaneous fatty tumors at the first meeting of this society. Two of them had been subjected to severe injury. Both had been blown up by high explosive shells in World War I. Fatty tumors developed rapidly, one within twenty-eight days after the injury. A series of tests were made on these patients, with the following results: 1. Examination of the visual fields showed narrowing of the fields for red in all 3 patients. 2. Roentgenograms of the sella turcica revealed defects in the clinoid processes in 2 patients. A relatively small pituitary gland was found in the third patient. 3. Dextrose tolerance tests showed that these patients could absorb large amounts of dextrose without its showing in the urine. Microscopically, no nerve tissue was observed in the excised fatty tumors, which showed a fibrous capsule and a fibrous stroma and fat cells. New methods of staining nerve fibers were not used. These patients were weak. The color of the skin had changed from white to a dirty chocolate, and they were mentally depressed. They could not work. Two had slight exophthalmos. The symptoms did not fit exactly into the diagnosis of Dercum's disease (*adiposis dolorosa*).

DR. SAMUEL AYRES JR.: I am glad to have heard Dr. Lindsay's discussion, because I have felt that an endocrine factor was present in this case, as the sudden exacerbation of the disease followed accidental injury. I have not established any abnormality in the patient's dextrose tolerance. He complains of weakness and of stiffness in his joints. The tumors themselves do not seem particularly tender, although that symptom may develop later. A careful investigation of the endocrine glands might be helpful.

**A Case for Diagnosis (Intraepidermal Epithelioma? Erythroplasia of Queyrat?).** Presented by DR. J. WALTER WILSON.

T. T. S., a white man of American stock aged 63, noticed a small lesion near the urethral meatus eight years ago. It was burned off once with an "electric needle," which produced a spark. The lesion shortly healed but reappeared at once and gradually spread until its present size was attained. The patient has always been in good health. Tests for the presence of a syphilitic infection were carried out several times, including examination of the spinal fluid, but the results were consistently negative.

Not only was the clinical appearance puzzling, suggestive of a type of lymphoblastoma to a number of competent dermatologists, but the same type of diagnosis (i. e., leukemia and Hodgkin's disease) occurred on at least two occasions to a hematologist as the result of studies of the blood, and again a diagnosis of lymphoblastoma was suggested by the observations in at least one of the histologic sections.

It is conceivable that the generalized pruritic eruption with inflammatory hypertrophy of the face, ears and nose in our patient may represent a bizarre complication of senile pruritus, with the hypertrophy having resulted from an excessive degree of itching and scratching.

Probably the most curious element in the whole picture is the fact that the condition did not recur when the hormone was discontinued. It would almost appear as though the hormone given over a relatively brief period (four months) could initiate physiologic processes which could continue under their own impetus. The situation may be analogous to that of a pendulum of a clock which has run down. Even after the clock has been rewound it is necessary to swing the pendulum by hand in order to start it going again. Perhaps the stimulus of the testosterone in this case was capable of reviving some physiologic mechanism, even though that stimulus was later withdrawn. Such a situation would be contrary to the observations of Dobes, Jones and Franks<sup>3</sup> in the treatment of senile pruritus with testosterone. They observed a tendency of the disease to recur after cessation of treatment. They also failed to secure benefit from the oral administration of testosterone, but obtained favorable results in 7 of 10 patients when the drug was given by injection or inunction.

Hollander and Vogel<sup>4</sup> also reported good results from the daily inunction of 4 mg. of testosterone propionate in a series of 8 cases of what they considered to be senile pruritus and even in several cases of recalcitrant eruptions following known externally irritating factors. There was a tendency to relapse on discontinuance of treatment, although several patients were reported as having remained well. The period of observation, however, was not stated.

Feldman, Pollock and Abarbanel<sup>5</sup> reported a series of 16 patients, both male and female, suffering from senile pruritus, with and without dermatitis. Of the 16 patients good results were obtained in 12,

3. Dobes, W. L.; Jones, J., and Franks, A. G.: Testosterone Propionate in Treatment of Senile Pruritus, *J. Clin. Endocrinol.* 5:412-418 (Dec.) 1945.

4. Hollander, L., and Vogel, H. R.: Testosterone Propionate in Treatment of Male Postclimacteric Dermatoses, *Arch. Dermat. & Syph.* 45:356 (Feb.) 1942.

5. Feldman, S.; Pollock, J., and Abarbanel, A. R.: Treatment of Senile Pruritus with Androgens and Estrogens, *Arch. Dermat. & Syph.* 46:112-127 (July) 1942.

## ABSTRACT OF DISCUSSION

DR. MARCUS R. CARO, Chicago: Dr. Ayres is to be congratulated on the response to treatment that he obtained in this strange case. The improvement is more gratifying because of the advanced age of the patient and the long duration of his alopecia, since both factors generally have an adverse effect on the results.

A positive finding is always more significant than a negative one. Waisman and Kepler reported in 1941 on a study of 138 cases of alopecia areata in which they observed no abnormality of function of the endocrine glands. If one may assume in the case being presented today that the response to treatment with methyl testosterone indicates a causative endocrine disturbance, the case takes on considerable importance.

In spite of the simultaneous improvement in the alopecia and the cutaneous lesions, I cannot be certain that they all are part of one symptom complex. I have never seen a case that parallels this one, but on examination of the photographs it is suggested to me, as it was to Dr. Ayres and Dr. Jensen, that there may have been a combination of senile pruritus, rosacea and possibly seborrheic dermatitis, with changes in the nails secondary to scratching and infection.

The histologic sections showed cystlike structures with a polymorphous infiltrate about them, such as are often seen in rhinophyma. The presence of such a wide variety of cells in the infiltrate speaks strongly against a diagnosis of lymphoblastoma.

I am grateful to Dr. Ayres for this presentation and for calling my attention to methyl testosterone in the treatment in hitherto discouraging cases of alopecia totalis.

DR. GEORGE C. ANDREWS, New York: I am rather sure that testosterone is of no use in the treatment for alopecia totalis in women. I have treated 2 patients thoroughly and carefully with it without noting any improvement.

DR. SAMUEL AYRES JR., Los Angeles: I want to thank the discussers. I presented this case with a good deal of hesitation because I know that one is always assuming some risk when one presumes to present what appears to be an unusual clinical entity, and I am not certain that this is more than a coincidental combination of symptoms. Yet the striking response of all of the patient's symptoms to the one therapeutic agent, together with the encouraging communication I received from Dr. Tobias, in which he stated that he had an identical type of case, led me to present it. I questioned Dr. Tobias in detail, and apparently his case coincided in every respect with mine, including the favorable response to treatment. It may be that there is some peculiar manifestation of the male climacteric which can produce a picture of this sort.

It was particularly striking, again, in view of the reaction of practically every one who saw this patient. Hardly any of the dermatologic staff questioned the likelihood that this was a case of some peculiar form of lymphoblastoma, and that again makes it more interesting in view of the therapeutic response.

March 1944 she has had an intensely pruritic, generalized vesicular and bullous eruption with exacerbations and remissions, for which she has twice been hospitalized. The lesions appear on an erythematous base, singly and in groups.

The patient appears moderately nervous and is underweight. Erythematous plaques with raised borders are present on the trunk, the arms and the neck. The patches vary in size; many have an annular appearance. Superimposed on them are thin-walled, tense vesicles and bullae; the latter are more numerous and of greater size in the axillas. The gums are reddened, tender, swollen and hemorrhagic along the dental border. Maxillary sinusitis of allergic origin is also present.

The blood count showed 11,000 to 20,000 white cells, with 5 to 6 per cent eosinophils and mild secondary anemia; fluid from a bulla contained approximately 75 per cent eosinophils. The iodide patch test gave a positive reaction. Blood tests for syphilis gave negative reactions.

In a report on the study of microscopic sections which was carried out by members of the staff of the Army Medical Museum (slide no. 8266 of the Hoff General Hospital), the opinion was expressed that a possible diagnosis of pemphigus foliaceus should be considered because of the presence of a type of acanthosis characteristic of that disease.

Treatment has consisted of injections of the patient's own blood; administration of crude liver extract, sulfapyridine, pamoquine naphthoate ("plasmochin") and penicillin, and a low protein diet, measures which resulted at best in moderate improvement, followed by early relapse.

#### DISCUSSION

**DR. SAMUEL AYRES JR.:** The case seemed to me a typical instance of dermatitis herpetiformis. The cause of this disease is a matter of considerable debate. It may be a form of an allergy, possibly endogenous. I think there is an allergic background in this case. The patient has had congestion of the nose for some time. The therapeutic problem in dermatitis herpetiformis is notoriously difficult. In the past one and a half years I have had 4 or 5 patients under treatment with hapamine (a chemical combination of histamine and despeciated horse serum globulin). I have felt that better results were obtained with use of this drug than with any other measure; although I do not believe that any patients are cured, there is a considerable degree of improvement.

#### Multiple Benign Cystic Epithelioma. Presented by DR. SAMUEL AYRES JR.

C. A., a white woman aged 39, has had a facial eruption which she thinks has been present since the age of 6 or 7 and has slowly progressed. None of her 6 sisters and brothers has had a similar disease.

The eruption is located on the face, especially the sides of the face, on the temples, in front of the ears and along the sides of the nose. The lesions consist of two types: numerous white, milium-like bodies, some of which show dark centers, resembling comedones, and, scattered among these, numerous smooth, rounded, pearly, elevated nodules, the size of a pinhead to that of a pea, having a somewhat translucent appearance and showing telangiectases. Some of these larger nodules show milium-like bodies within them. There are a number of small, pitted scars. No pustules or ulcerations are seen.

Treatment, performed elsewhere, has consisted in the application of an "electric needle" to a few lesions, with unsatisfactory results.

#### DISCUSSION

**DR. SAMUEL AYRES JR.:** The diagnosis rests finally on the histologic study of a specimen, which is not yet available. The disease is rare and apparently of nevoid origin, appearing in late childhood or early adolescence. Adenoma sebaceum should possibly be considered in the differential diagnosis, but the transparency of the nodules conforms rather well to benign cystic epithelioma.

**NOTE:**—Histologic examination of a nodule revealed the characteristic structure of multiple benign cystic epithelioma, with proliferation of the basal cells in long, narrow strands with cystic formation.

induratum in middle-aged persons, published in 1909, opened fresh ground in the study of hypodermic nodules of the lower limbs. Later he turned his attention to the study of autolytic processes underlying the production of eczematous lesions, which he elaborated in his Lumleian Lectures at the Royal College of Physicians in 1921 and at the International Congress of Dermatology in Copenhagen, Denmark,



ARTHUR WHITFIELD, M.D.  
1868 - 1947

in 1930. He also wrote on many other subjects, which are too numerous to mention here.

He held many offices in the dermatologic societies in his own country and was a member of a number of foreign societies. He was proud of his corresponding membership in the American Dermatological

## Society Transactions

### LOS ANGELES DERMATOLOGICAL SOCIETY

Clement E. Counter, M.D., *Chairman*

Maximilian E. Obermayer, M.D., *Secretary*

Nov. 13, 1945

**Adenoma Sebaceum, Pringle Type.** Presented by DR. H. C. L. LINDSAY.

**Erythema Induratum and Sarcoidosis (with Erythema-Annulare-Like Lesions).** Presented by DR. MOLLEURUS COUPERUS.

B. M., a white woman aged 59, born in the United States, had been in fairly good health until three years ago when a gangrenous appendix was removed. At the time it was noted that the spleen was palpable 2 fingerbreadths below the costal margin. While the patient was in the hospital there developed abscesses in the eye, which resulted in glaucoma and subsequent loss of sight in both eyes. On both legs scaling plaques developed, which after many months disappeared, leaving no trace. Four months ago the present eruption developed, accompanied with a mild burning sensation.

On the back and front of both legs there are annular and oval lesions, some 10 cm. long and 5 cm. wide, consisting of a fine erythematous, 3 to 4 mm. wide, barely palpable, slightly elevated border and a more or less normal-appearing center, suggesting erythema annulare centrifugum. The lesions are not tender, and no loss of sensation is discernible.

The eyeballs protrude from their sockets, are irregular in contour and seem to contain many cysts and perhaps small abscesses. Both eyes are insensitive to light. The spleen is firm and enlarged to below the level of the umbilicus.

The Wassermann and Kahn reactions were negative. The leukocyte count was 2,800 with 17 per cent lymphocytes on one occasion and 1,500 on another. Roentgenograms revealed that the chest and the long bones of the hands were normal.

Histologic examination of one of the lesions performed in December 1943 showed the features of sarcoid of Boeck. Examination of a specimen recently removed from the border of one of the present plaques disclosed that the epidermis was somewhat irregular and acanthotic in one area but otherwise essentially normal. The upper part of the dermis showed a mild lymphocytic perivascular infiltrate. Between the fat cells of the hypoderm was a heavy infiltrate of epithelioid cells and lymphocytes. This infiltrate extended in two areas up to the sweat glands. Just above the hypoderm there was some tubercle formation, but only two or three giant cells were present in the sections.

#### DISCUSSION

DR. L. H. WINER (by invitation): Clinically I could see no features in favor of a diagnosis of erythema induratum. The lesion resembled sarcoid. The histologic picture was interesting in that the epidermis and connective tissue were not involved, but the subcutaneous fat was implicated in a process in which the fat was being replaced by infiltration. Apparently these are old lesions and could represent the final stage of old erythema induratum, considering that erythema induratum is a tuberculous thrombophlebitis in the subcutaneous fat and that replacement

## CLEVELAND DERMATOLOGICAL SOCIETY

L. L. Praver, M.D., President

G. W. Binkley, M.D., Secretary and Reporter

Oct. 25, 1945

**Reticuloendotheliosis (Letterer-Siwe Disease).** Presented by means of color photographs by DR. MARGARET JANE ADDISON (by invitation), Boston.

J. W., a white infant aged 8 months, was admitted to Babies and Childrens Hospital. At birth there were diffuse petechiae on the trunk and hands. They underwent remission during treatment with vitamin K. The child ate well, but always cried and was never able to sit up. Later the skin showed crusted lesions, then bullous lesions. The parents noted a contrasting chalky white appearance of the skin.

The mother and father were well; the mother had had rheumatic fever in 1939. There were 3 healthy siblings, aged 8, 6 and 3 years.

On his admission, on June 20, 1945, petechiae were seen on the trunk, being most numerous on the upper part of the back and the occiput. There were several large bullae on the buttocks and the inner surfaces of the thighs. They averaged 2 cm. in diameter and contained serous fluid. The skin of the trunk and head showed much yellow desquamation.

The heart and lungs were normal. The abdomen was greatly distended and tender on palpation. The liver was hard on palpation and was enlarged 4 to 6 cm. below the costal margin. The spleen was hard and enlarged 4 to 5 cm.

The hemoglobin content was 38 per cent (Sahli). The erythrocytes numbered 2,240,000 and the leukocytes 10,500, per cubic millimeter, with a distribution of 77 polymorphonuclear leukocytes, 20 lymphocytes, 2 monocytes, and 1 eosinophil. The platelets numbered 450,000. The bleeding time was four minutes and fifteen seconds; the clotting time was thirteen minutes. The prothrombin time was eight minutes.

The patient died on the twenty-first day in the hospital.

This case will be published in full later.

## DISCUSSION

DR. H. N. COLE: Through the courtesy of Dr. John Toomey, this patient was seen in consultation. The child was very sick, with high fever, and presented the picture, shown in the lantern slides, of an enormous swelling in the upper quadrants of the abdomen due to hepatosplenomegaly. The skin, particularly that of the trunk, had a brown tint of varying shades, probably due to disintegrating hemoglobin. The eruption involved the trunk particularly and was made up of telangiectases, in some places confluent. There were scattered papulosquamous lesions, occasional small vesicles and bullae, crusted areas and small atrophic areas, where lesions had healed. Palpation of the skull revealed no areas of softening. It was felt that the case fell in the group of lipidic reticuloendotheliosis and that, while the child was not Jewish, it was perhaps an instance of Niemann-Pick disease. Further chemical studies of the blood were suggested. Not long afterward the child died, and autopsy studies, in Prof. Howard Karsner's department, revealed a nonlipidic reticuloendotheliosis, known as the Letterer-Siwe syndrome. The disease is characterized by progressive anemia, hemorrhagic diathesis, hepatosplenomegaly, greatly enlarged lymph nodes, fever and frequent osseous involvement. Abt and Denenholz (Letterer-Siwe's Disease; Splenohepatomegaly Associated with Widespread Hyperplasia of Nonlipoid-Storing Macrophages: Discussion of So-Called Reticulo-Endothelioses, *Am. J. Dis. Child.* **51**:499-522 [March] 1936) reported the ninth case of this disease, and this patient is the tenth. Wallgren (Systemic Reticuloendothelial Granuloma, Nonlipoid Reticuloendothelioses and Schüller-Christian Disease, *Am. J. Dis. Child.* **60**:3, 471-500 [Sept.] 1940) wonders whether nonlipid reticuloendotheliosis and Schüller-Christian disease are not identical and whether so-called infectious reticuloendo-

throughout and absent in some areas. The prickle cell layer was of normal thickness in some areas, while in others the tips of the papillae approached the granular cell layer closely. There were hair follicles rather closely set, and follicular plugging was seen in some of them. The dermis was the seat of diffuse round cell infiltration with some perivascular and perifollicular localization, but it was located to the greatest extent around the sweat glands. There was decided dilatation of blood vessels extending deep into the dermis. The connective tissue elements were normal. Some smooth muscle of normal appearance was seen.

While the patient was in the Army the disease was treated with various fungicidal preparations, but no improvement was obtained.

#### DISCUSSION

DR. HAL E. FREEMAN: Pityriasis versicolor leprosy, ordinary vitiligo, leukoderma and achromia parasitica have been ruled out. The possibility of dermatitis factitia cannot be excluded. The inflammation which is present appears to be secondary. The hypopigmented areas develop first and the inflammation later, a fact which makes me think that the lesions may be self imposed.

DR. ANKER K. JENSEN: I would suggest that lepromin and histamine tests be performed.

DR. M. E. OBERMAYER: I have no diagnosis to offer, but I should like to point out the valuelessness of using nasal scrapings in investigating lepra. While involvement of the nasal mucosa is fairly common in lepromatous lepra and mycobacteria can be demonstrated with ease in nasal scrapings in such cases, it is not uncommon to find acid-fast diphtheroid bacilli morphologically indistinguishable from *Mycobacterium leprae* in the nasal mucous membrane of healthy persons and lepers. Consequently, the presence of acid-fast bacilli does not mean that the subject has lepra nor does their absence indicate freedom from the disease.

DR. NELSON PAUL ANDERSON: I have seen 1 or 2 similar cases. A search for fungi and other causative agents is fruitless. I believe that this disease is some form of bacterial infection, probably of a low grade type. There is something about it that does not fit in with a fungous infection.

DR. SAMUEL AYRES JR.: There was something about the lesions on the forehead which appeared different from those in other areas. I would not be surprised if the eruption would eventually prove to be lymphoblastoma.

DR. A. F. HALL: I think that Dr. Freeman's suggestion of dermatitis factitia must be kept in mind. That is the only diagnosis that I can conceive of consistent with the history of these lesions and their appearance. I am not familiar with any fungous infection which would cause a primary depigmentation followed by squamous manifestations rather than in the reverse order. I can conceive of the application of a bleach, such as solution of mercury bichloride, to an area with resultant depigmentation and further applications of the same chemical resulting in an inflammatory reaction followed by scaling. This patient has a rather apprehensive mien, and there is something strange in his attitude toward his dermatosis that I am not able to define or interpret. The flare reaction to histamine was normal. Pinta might be possible, except that the negative reactions in the blood tests militate against it. There has been no dark field examination of scrapings.

Hemangiomas of the Scrotum (Angiokeratoma of Fordyce?). Presented by DR. SAUL S. ROBINSON and DR. SAMUEL TASKER (by invitation).

R. N., a white man aged 61, noticed the development five years ago of lesions on the scrotum, which slowly increased to the present size. There are no symptoms.

be seen on the arms. There is a small group of pustules far back on the left buccal mucous membrane. There is a mild generalized swelling of the lymph nodes and the postcervical region. His temperature (oral) was 99.2 F. at noon. The differential blood cell count was essentially normal.

#### DISCUSSION

DR. NELSON PAUL ANDERSON: I hesitate to open the discussion in the presence of Dr. Goeckerman and Dr. Wilhelm, who were the first in this country to report the varicelliform eruption of Kaposi. I would accept that diagnosis in this case with a good deal of reservation. The lesions of Kaposi's varicelliform eruption while not particularly limited to the areas of atopic dermatitis are worse in those areas. I have known persons with this disease to be decidedly sick, although my observations were made before the introduction of treatment with penicillin. However, a few patients have been given sulfonamide drugs, which apparently had little if any effect. Not having seen this patient when the disease was severest, I can suggest only that this patient may have had chickenpox, even though chickenpox is uncommon in adults who live in a large city. You are all aware of the work that has been done to establish the herpes virus as the cause of this eruption. The boy gives a history of recurrent aphthous stomatitis for a number of years.

DR. W. H. GOECKERMAN: I agree with Dr. Anderson that this is not Kaposi's eruption. The lesions are manifestly discrete except for the atopic dermatitis, which necessarily would eliminate the diagnosis. Whether vaccinia, chickenpox or some other infectious disease was superimposed on the atopic dermatitis is now somewhat indefinite. The history would suggest that it was. I have been intrigued by the fact that when we reported our first case nine or ten years ago I was unable to find a single report of this disease in the American literature. Now suddenly there are reports from two sources of a number of cases of this eruption seen at the same time. It is possible that such cases are seen by general clinicians or pediatricians without being recognized. However, they present a distinct clinical picture. In recent years almost any eruption the cause of which cannot be explained otherwise is said to be due to a virus. I am still skeptical about this. The intriguing question to me is whether virus of various types is becoming more virulent than it was in years past.

DR. SAUL ROBINSON: I believe that this patient is suffering from pityriasis varioliformis acuta. The onset with fever and constitutional symptoms together with papular, vesicular, necrotic and hemorrhagic lesions has been reported to occur in the cases of acute disease.

DR. SAMUEL AYRES JR.: I have seen 2 cases, both in small children, but the eruption was almost confluent over the areas of atopic eczema. This patient presents no such picture. Instead the lesions are sparsely distributed. If he did not have eczema I should say that he had chickenpox. The patient, however, says that he has had chickenpox in the past.

DR. J. R. SCHOLTZ: I have read Dr. Goeckerman's paper and others, and I am not certain of the criteria on which this diagnosis is established. In the Army, among men vaccinated against smallpox routinely, we saw a number of men with chronic neurodermatitis who soon experienced generalized vesicular and pustular eruptions, more severe on the areas of chronic dermatitis and accompanied with a high temperature. It would seem that the clinical picture and the course of the disease might be determined by the type of virus that causes the infection. For

DR. J. R. DRIVER: When this patient came under our care, there was no question but that the disease was pemphigus erythematosus. This type of pemphigus can develop into pernphigus foliaceus or into any other form as an end result. This has never happened in any other case of pemphigus erythematosus that I have seen.

**Dermatitis Repens.** Presented by DR. J. H. BARR JR. and DR. J. KAM for DR. H. N. COLE and DR. J. R. DRIVER.

M. P., a white woman aged 77, in December 1944 first noted an erythematous, pustular, scaly eruption on the dorsa of the first two toes of the right foot. Within two weeks similar lesions appeared on the left foot. This eruption has gradually extended. In March 1944 a diagnosis of stasis dermatitis of the right leg was made.

There is a symmetric eruption involving the first three toes and the adjacent dorsal and plantar surfaces of each foot. The patches are fiery red and well defined, with irregular, scaly, undermined borders. The surface of the areas is covered with phlyctenular pustules, some of which have ruptured and become covered with superficial crusts. On the lower third of the leg and the dorsum of the foot on the right side the skin is fiery red, edematous, infiltrated and scaly. In the region of the right lateral malleolus there is a healing ulcer.

The hemogram and urine were normal. Cultures from cutaneous lesions revealed a hemolytic *Staphylococcus aureus* which was coagulase negative.

Biopsy of tissue from the sole of the right foot revealed slight acanthosis, absence of the stratum granulosum and lymphocytic infiltration, with microabscess formation.

Treatment consisted of superficial roentgen irradiation, dressings and sclerosing injections of the varicose veins. The eruption did not respond to therapy and now is similar to the process on the feet. Tyrothricin in a concentration of 33 mg. per hundred cubic centimeters of distilled water; penicillin ointment; local application of an aqueous solution (1:3,000) of zephiran chloride and intramuscular injections of sodium penicillin were used, with some improvement.

#### DISCUSSION

DR. E. W. NETHERTON: It is difficult to rule out a diagnosis of psoriasis. This is one of the cases no one agrees about. The patient does not have any lesions in the areas of predilection for psoriasis. The lesions on the soles and the toes certainly looked like those which in the past have been called pustular psoriasis, the resistant type.

DR. H. N. COLE: The biopsy specimen was taken from a lesion on the foot. When this patient was first seen, the lesions had the typical fringelike extension with overhanging margin and pus under them. The cultures showed the staphylococcus. We thought of the possibility of a pustular type of psoriasis, but in view of the chronicity we felt it belonged with dermatitis repens rather than with pustular psoriasis. There are some places on the feet which still show this type of lesion.

**Recalcitrant Pustular Eruption on the Extremities.** Presented by DR. G. W. BINKLEY.

The twin sister of C. P. L., a white woman aged 57, with a resistant pustular eruption on the extremities, has had the same disease, but in milder form, on the hands for thirty years and on the feet for the past six to twelve months.

A pustular eruption of the extremities has been present in a cyclic occurrence for five years. It has resisted all external treatment except for a short remission from superficial roentgen irradiation. There was a small amount of itching during September, when a thick, piled-up crust was present. There are no subjective symptoms now. The nails of the great toes were removed six years ago.

Dr. J. R. SCHOLTZ: Clinically the lesion feels and looks like chronic granulation tissue. I am not familiar with staphylococcal infection which continues for three years without change and without moving to a new location. I also do not believe that the anatomic situation would permit the development of a lesion like this on the basis of a lymphatic blockage.

DR. HAL E. FREEMAN: I would like to have the presenter rule out granulositis rubra nasi.

DR. W. H. GOECKERMAN: I should like to see this case presented again at some future date. There is no doubt that the whole behavior of the disease is atypical if it should prove to be a so-called solid edema.

DR. WILLIAM MULVIGHILL: I suggest the diagnosis of lupus vulgaris tumidus. The microscopic picture is not typical, but there are sufficient features to suggest that diagnosis. The section might be from an area that did not show the typical granulomas of lupus vulgaris. The infiltration with epithelioid cells is enough basis for consideration of one of the true granulomas.

DR. L. H. WINER (by invitation): I agree with Dr. Obermayer's diagnosis of elephantiasis nostras and not lupus vulgaris tumidus. Lupus vulgaris is a disease that begins in early childhood and not as a rule in a mature man. There are no lupus nodules here. Clinically this tumor suggested a hemangioma or lymphangioma, but histologically there were only a few small capillaries in an extensive fibrotic process, which could be the result of an old chronic inflammation. These fibroses are not as hard as those of a keloidal scar.

**Balanitis Xerotica Obliterans.** Presented by MAJOR RICHARD L. SAUNDERS, Medical Corps, United States Army, Birmingham General Hospital (by invitation).

A soldier aged 27 noticed in July 1942 a painful and tender swelling of the glans penis. Since then the inflammation has been progressive, with alternating remissions and exacerbations. Sexual intercourse has been impossible for the last two months because of the pain. Various local applications have been of no benefit.

On the right side of the glans penis and the corresponding area of the inner layer of the prepuce there is an indurated plaque of firm consistency, purplish borders and an eroded surface.

Histologic examination of the lesion showed an atrophic epithelium with intracellular edema and liquefactive degeneration of the basal layer. Immediately under the epidermis was a thick band of hyaline cellular tissue. Intermingled in the deeper parts of the dermis were foci of infiltration of lymphocytes, plasma cells, a few polymorphonuclear leukocytes and monocytes and many small blood vessels.

#### DISCUSSION

DR. SAMUEL AYRES JR.: Lesions of this sort on the penis present a difficult problem in diagnosis. In this case the history was of the foreskin's being rather adherent and not easily retracted until a comparatively short time ago. Apparently a chronic irritative process had been present for several years, resulting in the present atrophic and hyperplastic changes. There is an appearance suggestive of leukoplakia. At the same time some thickening suggests the possibility of early malignant change. I am in doubt as to whether the disease should be definitely classed as balanitis xerotica obliterans. The few cases I have seen have usually started around the meatus and have resembled lichen sclerosus et atrophicus. I am not convinced that this is a true case of balanitis xerotica obliterans. I would suggest the possibility of leukoplakia with early malignant change. I think complete excision is the treatment of choice.

The eruption is symmetric. It involves the hypothenar area of the palms, the heels, the midesoles and the toe nails. The primary lesions are two: a clear-serum-containing vesicle, which dries in situ to a shellac-colored, semitranslucent, horny scale; and a round, slightly elevated, light yellow pustule. The lesions are always small, from 1 to 4 mm., and are located in the epidermis. The great toes show sclerosis of the epidermal tissue after surgical removal. The nail of the left third toe is thick, dry and friable in the distal portion. The nail of the right third toe is deeply grooved transversely. Examination by an internist revealed no discernible organic disease.

Microscopic study of material from a pustule showed well preserved leukocytes but no bacteria. The epidermis, macerated in 10 per cent potassium hydroxide, showed no spores or myceliums. A hemogram showed 4,190,000 erythrocytes and 13.5 Gm. of hemoglobin per hundred cubic centimeters. A roentgenogram of the fingers and toes showed nothing abnormal in the bones or joints. An intradermal injection of trichophytin, 1:30, and oidiomycin, 1:100, gave a normal reaction. The 17-ketosteroid content of a twenty-four hour specimen of urine measured 10.4 mg.

A histologic section of skin from the foot showed zones of parakeratosis limited to the sites of the severe cellular infiltration in the corium. In the rest of the epidermis the stratum granulosum was of normal thickness. In places there was mild acanthosis, which thinned out over the pustules. The basal layer was intact everywhere.

The infiltrate was of pure monocytic type, dense and packed against the basal layer. Moderate perivascular cuffs of infiltrate were present in the entire upper portion of the corium.

No response was obtained to treatment for one week with intramuscular injections of penicillin in oil and beeswax.

#### DISCUSSION

DR. E. W. NETHERTON: The lesions on the heels are clinically like the ones seen in resistant bacterids. On the sides of the foot are orange-colored blisters, which look as though they might peel off. The eruption resembles a dermatophytosis, but I am sure that Dr. Binkley would have found the organism if it were present. It is difficult to settle whether it is a fungous infection or a reaction to infection elsewhere.

DR. G. W. BINKLEY: No foci of infection were found. The tonsils are small, and no apical abscesses were found on roentgenographic examination of the teeth. The gallbladder was not studied. The intradermal test with trichophytin gave a negative reaction. There is no clinical or laboratory evidence of a fungous infection in this case. Perhaps the family history should be emphasized. The patient has a twin sister who exhibited a similar type of disturbance, though of minor intensity, at the age of 27. It was reported to me that she used many antiseptics, with no results. She still has lesions on the palms and soles, but because they are never in great number she has never consulted a dermatologist. I regard this eruption as a metabolic disturbance primarily, but the possibility of a focus of infection must be kept in mind.

**Late Chronic Lymphogranuloma Venereum with Elephantiasis.** Presented by DR. J. H. BARR JR. and DR. J. KAM.

E. N., a Negro aged 29, had a "bubo" in the right inguinal region in 1937. This ruptured, with the formation of multiple sinus tracts. During 1940 there was intermittent swelling of the penis and scrotum. At that time the diagnosis of lymphogranuloma venereum was made. In January 1945 severe edema of the penis and scrotum appeared and has persisted.

In the right inguinal region there are multiple scars. The scrotum is greatly enlarged. The skin is thickened and edematous. The testes are apparently normal. The architecture of the penis is distorted, and it is many times normal size. There

DR. L. H. WINER (by invitation) : I observed some of these chronic verrucous lesions to contain amyloid histologically. When it is not seen in a section that does not mean it is not there. When the section is stained with methylrosaniline chloride but Canada balsam or levulose, which is acid in reaction, is used to cover it, the bright red color is destroyed. The test of injecting congo red directly into the lesion is of more definite value. A number of cases have been presented which histologically did not show amyloid at first presentation because of the difficulty in staining.

DR. M. E. OBERMAYER: Disregarding the damage from irradiation, with which we are all in agreement, the clinical appearance of the eruption is suggestive of two diseases: localized amyloidosis and lichen ruber moniliformis. The former can be ruled out by the absence of amyloid (and I am glad of Dr. Winer's reminder as to the superiority of injections of congo red over staining the sections in determining the presence or absence of the substance). The latter diagnosis is supported by the histologic observations, which are almost identical with those in the case of Dr. Miller and Dr. Wilson recently published in the ARCHIVES OF DERMATOLOGY AND SYPHILOLOGY. If one examined the patient carefully one must have noticed the original eruption in the form of waxy striate papules, for which roentgen rays were administered. While this eruption is highly suggestive of lichen ruber moniliformis, I must admit that the papular form of dry neurodermatitis may at times imitate it closely. The intensive pruritus and the psychoneurotic features of the patient's personality, which did not escape my observation, are in line with such a suggestion. Yet, I favor the diagnosis under which the patient was presented.

**Cheese Mite Dermatitis.** Presented by DR. N. P. ANDERSON.

B. B., a white man aged 21, a food processor by profession, noticed three weeks ago the appearance of a severely pruritic eruption on the flexor surfaces of the arms and forearms which developed after the unloading of several boxes of cheese on a hot day.

He presented an eruption on the aforementioned areas which at first glance appeared to be scabies. Closer examination revealed numerous erythematous wheal-like lesions capped with a minute pinhead-sized vesicle.

Cheese mites (*Tyroglyphus longior*) were easily demonstrated from a sample of cheese. A slide containing the animal parasites was demonstrated.

DISCUSSION

DR. C. RUSSELL ANDERSON: This recalls an interesting case that I saw recently in a woman who had dermatitis over a scar in the region of the right breast, which had been removed because of carcinoma. She had a device made of sponge rubber to fill in the defect. She worked as a draftsman, and when she was bending over the table this false breast would rise up and make her appear lopsided. She therefore removed the sponge rubber and filled the brassiere with rice. This would drop when she bent over, and the false breast would remain in a natural position when she rose up. Three or four days later a papular dermatitis developed, which at first glance resembled carcinoma *en cuirasse*, but each papule had a punctum in the center. The rice was found to be infested with mites.

MAJOR R. L. SAUNDERS (by invitation): In grain processing centers, where all types of cereals are made, grain mites are common. The grain men call them "tumbling grain." In susceptible persons it produces a dermatitis due to *Tyroglyphus farinae*.

are multiple sinus tracts, which discharge pus and urine. At the base of the penis and over the adjoining scrotum there are multiple papillomatous growths. In one area there is a dusky red, slightly elevated, well defined patch.

The Kline reaction of the serum was negative. The urine contained many bacteria, erythrocytes and leukocytes. The hemogram was normal. Impression smears from selected tissue were questionably positive for Donovan organisms. Intracutaneous tests with Frei and Ducrey antigens gave positive reactions. The serum globulin was elevated.

Histologic examination revealed a slight acanthosis with exudate rich in neutrophilic leukocytes at the sites of epithelial erosion. In the corium there were numerous lymphocytes, and in some areas large mononuclear cells and fibroblasts. No Donovan organisms were seen.

A suprapubic cystotomy and incision of the penis were performed. Sulfathiazole has been given orally, with no significant improvement.

#### DISCUSSION

DR. I. L. PRAVER, Columbus, Ohio: Would Dr. DeOreo tell us whether he has seen many cases of this type during his service in the Pacific?

DR. GERARD DEOREO: I have not seen many of these cases on the venereal service. The most outstanding feature of this case is the degree of involvement. The red, beefy color of the penis, which suggests granuloma inguinale, is present here.

DR. H. N. COLE: I think this is a remarkable case. We have never had a case of elephantiasis either at City or at Lakeside Hospital, but cases of elephantiasis in men have been reported. I think Biberstein made the first report on the syndrome, showing that it may be seen in the male as well as in the female. The patient has a positive reaction to the Frei test, but even if he had not I should be willing to make a diagnosis of lymphogranuloma venereum. One must also think of granuloma inguinale. Donovan bodies have not been found.

#### A Case for Diagnosis (Granuloma Pyogenicum?). Presented by DR. GEORGE M. STROUD.

The father of B. J. A., a white child aged 5 years, has a considerable number of large, slightly pigmented, fibrous nevi on the face. About three and one-half months ago the mother noticed a smooth red nodule on the child's right cheek. The lesion showed no apparent change until a week ago, shortly after the specimen for biopsy was taken, when the central end of the incision ulcerated, while around the peripheral edge there was slight clearing.

On the outer part of the right cheek there is a fairly sharply defined, slightly raised, indurated, dull red nodule, 2 by 2.5 cm. which blanches slightly on pressure. On the posterior border is a linear scar, leading centrally to an irregular, crusted ulcer. The regional submandibular lymph node is slightly enlarged and tender.

The hemogram and urine were normal. The Mantoux test gave a slightly positive reaction.

On biopsy the epidermis showed no primary change. In one edge of the section, deep in the dermis, was an area with an increased number of new vascular spaces, about the size of capillaries. The infiltrate around the vessels was moderate and contained cells with pale blue nuclei, somewhat similar to the cells lining the vessels, along with some lymphocytes and plasma cells and a few polymorphonuclear leukocytes. There was a similar perifollicular infiltrate. The collagenous tissue in these areas was pushed aside or displaced.

#### DISCUSSION

DR. G. W. BINKLEY: From a histologic study it is not possible to say what the original lesion was, but I am positive that it was not granuloma pyogenicum. Granuloma pyogenicum is pedunculated, sometimes fairly flat, but usually has a central artery supplying by branches many lobules of granulation tissue, in which

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## MYXOMATOUS DEGENERATION CYSTS OF SKIN AND SUBCUTANEOUS TISSUES

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DURING the early part of this century references to synovial cysts, ganglions, epidermal cysts and the like (this does not refer to epidermal or epidermoid cysts which are produced by epidermal inclusions following puncture wounds and are usually seen on the palmar surface of the hands) were frequently seen in dermatologic literature. The recent references are almost entirely found in surgical literature.

Since dermatologists are frequently called on to advise patients concerning these lesions, it seemed appropriate to review recent developments and report my work at this time. This report is based on the microscopic study of material from 58 cases and roentgen ray therapy in 105 cases.

Microscopic material was studied from myxomatous degeneration lesions in 38 cases of the wrist, 10 of the hand, 4 of the fingers, 4 of the foot and 2 of the ankle.

The study was originally planned and started in 1937 in conjunction with Dr. R. H. Denham, after a discussion in which I had related the ineffectiveness of surgical treatment of lesions of the fingers and he had reported the equally unsatisfactory results in treatment of the usual ganglions of the wrist. It was our belief that so-called synovial cysts of the fingers and ganglions were essentially the same type of lesions. A review of microscopic material from 58 cases, distributed as indicated, supported our belief. The histologic changes are essentially a cystic cavity in normal dermis or subcutaneous fibrous tissue. The lining wall is made up of flat fibrous tissue cells and shows no endothelial or epithelial lining membrane. There is no inflammatory infiltrate in or about the cavity. The cyst is filled with a clear mucinoid or myxomatous, gelatinous material. Early cysts show first a cystic degeneration of fibrocytes, with droplets of mucinoid material in the

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vial fluid outside the tendon sheath, (3) secretion of synovial fluid through small channels into surrounding connective tissue, (4) fetal sequestration of synovial membrane, (5) secretory activity of residual embryonic mesenchymal cells or reversions of fibrocytes to more embryonic forms with secretory activity and (6) myxomatous degeneration of fibrocytes.

Adventitious bursas and tendon sheath hernias are occasionally seen and would constitute a major differential diagnostic problem except that the fluid can usually be pressed out from the bursa or hernia back

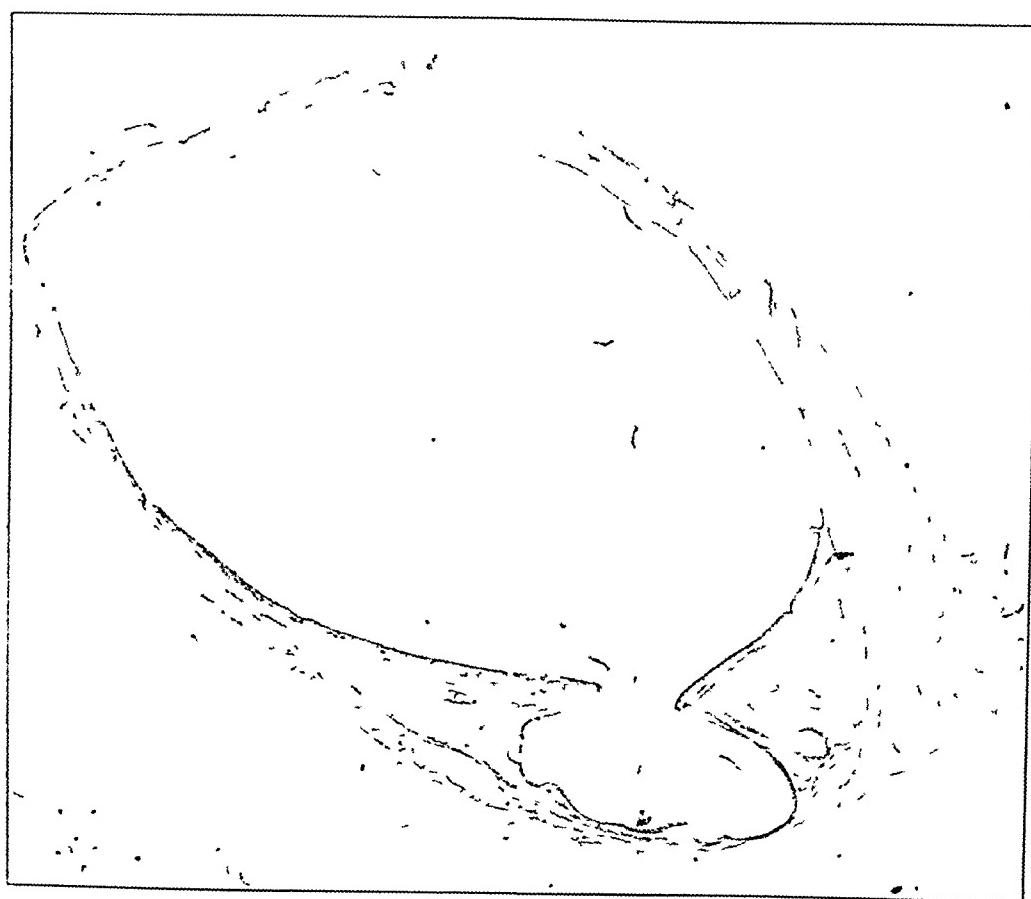


Fig. 2.—Microscopic picture of a cyst from the wrist, showing the multiple lesions which are so frequent.

into the rest of the local synovial system. This should also be true in herniation of tendon sheaths were it tenable. However, microscopic study of serial sections from these lesions shows no evidence to support any of the first four hypotheses since hernias, tears, channels or synovial membrane cannot be found. The recent literature and a critical examination of my pathologic material make untenable former hypotheses connecting these lesions with any synovial system. Ganglion, since it is merely a gross descriptive term (a hard globular swelling on a

Inasmuch as the patient had previously had only a small amount of roentgen irradiation, he was given additional roentgen radiation over the folds of his arms and over the sternal areas. The keratotic lesions were treated with solid carbon dioxide. For the dry skin a baby oil was prescribed.

#### DISCUSSION

DR. HERBERT H. JOHNSON: There appear to be two distinct, although overlapping, eruptions which occur from ingestion of quinacrine. One is an eczematoid dermatitis, which has the distribution of acute arsenical dermatitis. It comes on suddenly once the patient has become sensitized, and it may become an exfoliative dermatitis in the severer forms.

The other type of eruption resembles lichen planus. In some cases there were papular and hypertrophic lesions which were verrucous in nature, while in others only erythema and atrophy developed. In some cases both the eczematoid and the lichenoid reactions were present.

It appears that quinacrine must be taken for a long time for the lichenoid lesions to develop. Cases have been reported from all the theaters of war, including the African and Sicilian theaters, and a large number of papers will be published on this subject in the near future. It is a prolonged disease, and hospitalization may be a matter of nine months or more. A striking feature is the absence of sweating in the extreme cases, causing much discomfort. The return of perspiration is a good indication of improvement of the process; sweating usually starts first on the forehead and axillas and appears weeks later on other areas of the body.

DR. R. E. BARNEY: There were two other striking features in this case, the loss of hair and the hyperpigmentation on the trunk. Is the histologic picture in these cases compatible with a diagnosis of lichen planus?

DR. HERBERT H. JOHNSON: In the early cases pathologic changes similar to lichen planus are present. In a case showing both regressing and new lesions, biopsy of a new papule showed changes compatible with lichen planus. In the old papule there were a striking collection of melanin-containing stellate cells in the upper part of the corium, slight atrophy of the skin and round cell infiltration around the vessels.

The case presented here is one of the inactive form except for the absence of sweating. Most patients have a regrowth of hair ultimately.

DR. H. J. PARKHURST, Toledo, Ohio: I believe one has seen reactions like this due to the arsenicals. Was there any evidence of hepatic damage?

DR. HERBERT H. JOHNSON: There have been many hepatic function studies; there seems to be some impairment of hepatic function, although clinical hepatitis is unusual.

I wish to emphasize that prolonged administration of quinacrine is required to produce this disease, and the incidence is low. I do not think it will be a serious problem.

DR. E. W. NETHERTON: What is the treatment?

DR. HERBERT H. JOHNSON: It is expectant. The main thing in severe cases is to prevent secondary infection and allay pruritus.

DR. J. E. FISHER: Do these patients have as much itching as with ordinary lichen planus, and are there lesions of the mucous membranes?

DR. HERBERT H. JOHNSON: Pruritus is severe in most cases at some stage of the disease. Oral lesions are striking. The milder lesions are like the typical lesions of lichen planus. In the more severe involvement dense plaques and ulcerations may occur.

DR. R. E. BARNEY: Why cannot these cases be interpreted as lichen planus due to quinacrine? It is known that typical cases of lichen planus follow use of arsenicals.

Methods of treatment have been varied and in many instances unreliable in their results. The following list gives some of the common methods used: (1) excision, (2) incision and drainage, (3) excision of the top of the cyst, (4) incision and curettage, (5) chemical cautery with nitric acid, phenol, trichloracetic acid or the like, (6) electrocoagulation, (7) freezing with solid carbon dioxide, (8) injection of proteolytic substances and sclerosing solutions, (9) amputation and (10) roentgen ray or radium therapy.

Needless to say, any lesions in which this number of procedures has been advocated must be resistant to treatment by simple means or one simple effective method would have been generally accepted by this time.

A review of reports of various methods of treatment combined with personal experience may be summarized as follows:

Excision is effective if much surrounding fibrous tissue can be excised. When wide excision is carried out unsightly adherent scars are usual. Incision either alone or with cautery, curettage or drainage is regularly followed by recurrence. Caustics, such as the chemical caustics and solid carbon dioxide, do not destroy the lesion. Electrocoagulation is promptly followed by recurrence.

Ball<sup>6</sup> recommended the injection of the enzyme "caroid" (a proprietary digestant preparation of papau). However, results were uncertain, and soon reports of severe infection were published. Key<sup>6</sup> reported severe infection with sloughing of much tissue. He felt that since "caroid" could not be properly sterilized its contamination with proteolytic bacteria was responsible for his poor results. Injections with sodium morrhuate have been recommended,<sup>7</sup> but have been frequently followed by recurrence. Amputation is effective, but in most cases needlessly radical.

Following the suggestions of Ormsby<sup>8</sup> and Sutton<sup>9</sup> that radium or roentgen ray was most effective in treatment of synovial lesions of the fingers and believing from my pathologic study that ganglions were essentially the same type of lesions, I decided to treat a series of ganglions with roentgen rays.

Five patients were at first treated with suberythema doses, reaction being avoided entirely. Results with this method were entirely

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## ACTION OF SOAP ON THE SKIN

### IV. Action of a Soap Containing Little or No Lauric or Oleic Acid

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AND

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**I**N THE manufacture of soap, fats are chosen which contain either lauric acid or oleic and other unsaturated fatty acids in order that the final soap have satisfactory lathering, cleansing and physical properties. The fatty acid fraction of an average toilet soap usually contains from 11 to 12 per cent lauric acid and 38 to 40 per cent oleic acid and other acids of one double bond.<sup>1</sup> A satisfactory soap may be prepared which has more lauric and less oleic acid, such as coconut oil soap, or one which has less lauric and more oleic acid, such as olive oil soap. Gardiner<sup>2</sup> and Goldman<sup>3</sup> have stated that coconut oil soaps are more irritating to the skin than other soaps, and this is not an uncommon clinical observation. Soaps made from only olive oil have been thought to be relatively nonirritating to the skin. There has been little or no opportunity to observe the action on the skin of a soap containing neither lauric nor oleic acid, since a soap so prepared is relatively insoluble in water and has poor cleansing properties. This paper will present data on the action on the skin of a detergent which contains little or no lauric or oleic acid.

In the first paper of this series<sup>4</sup> the results of patch tests with the single fatty acids were reported. Among those fatty acids present in soap in any appreciable amount, lauric acid elicited the highest percentage of positive reactions to patch tests. Oleic acid elicited only a few positive reactions. During the past five years patch tests with the

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From the Department of Dermatology, Harvard Medical School, and the Massachusetts General Hospital.

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3. Goldman, L.: Patch Tests with Soaps, *M. Bull. Univ. Cincinnati* **7**:90-92 (Nov.) 1935.
4. Blank, I. H.: Action of Soap on Skin: I. Patch Tests with Fatty Acids, *Arch. Dermat. & Syph.* **39**:811-816 (May) 1939.

DR. HENRY E. MICHELSON, Minneapolis: There is no way of being certain, but I doubt whether more cases have occurred since insulin has been used. Certainly, the lesions do not disappear when insulin is given.

DR. JOHN F. MADDEN, St. Paul: I do not think I have ever seen the lesions disappear, regardless of what happens to the diabetes.

DR. FRANCIS W. LYNCH, St. Paul: Not much is known about the course of necrobiosis lipoidica diabetorum after prolonged good management of the diabetes. I wish all the old cases might be reviewed by one person.

**A Case for Diagnosis (Endarteritis Obliterans? Erythema Induratum?).**  
Presented by DR. JOHN F. MADDEN, St. Paul.

A. P., a woman aged 73, stated that in September 1945 dime-sized, erythematous, indurated plaques appeared on the medial posterior surface of the lower third of the right leg. Central vesicles developed, and in early October the plaques became gangrenous and ulcerated. The lesions enlarged until they became two fairly clean, deep, moderately painful ulcers, 4 by 6 cm. The pain was greatest at night. The patient stated that she had similar lesions on the left leg about thirty years ago, which healed after two or three months. Occasional lesions had occurred at intervals since that time, their sites now marked by scars. In 1938 she entered the Ancker Hospital for treatment of a similar ulcer, which healed in six weeks. Shortly after this, varicose veins of both legs were treated by injections. In 1944 two similar ulcers appeared on the right leg, for which she was hospitalized for five months.

Serologic reactions for syphilis were negative; the reaction to tuberculin was strongly positive. The sedimentation rate was 101 mm. in one hour. Roentgenograms showed an atrophic type of absorption taking place in the distal phalanx of the great toe. No evidence of infection of the bone was seen.

**DISCUSSION**

DR. RUBEN NOMLAND, Iowa City: I think the patient has obliterative arterio-vascular disease, and I have seen 2 patients with this disease who had ulcers of the leg. They were slow to heal because of the obliteration of the arteries, and I think them somewhat similar to stasis ulcers, with the addition of arterial closure.

**Adenoma Sebaceum (Pringle).** Presented by DR. JOHN F. MADDEN, St. Paul.

G. C., a girl aged 8 years, presented pinhead-sized, yellow papules associated with telangiectasia on the nose and the malar eminences shortly after birth. There was no knowledge of a similar eruption in any member of the family. The patient's mental development was normal.

The eruption, covering the nose and most of the cheeks, now seems to be spreading.

**DISCUSSION**

DR. STEPHAN EPSTEIN, Marshfield, Wis.: Superficial, cautious electrodesiccation is helpful, especially in treatment of the telangiectatic type presented by this child.

**Alopecia Cicatrisata (Pseudopelade).** Presented by DR. JOHN F. MADDEN, St. Paul.

Mrs. M. R., a housewife aged 45, stated that she began to lose hair in small spots on the crown of the head in 1942. There was no inflammation, discomfort, erythema or scale associated with the lesions.

Patches of atrophic scarring, the size of a pea to that of an olive, with loss of hair are present over most of the crown.

The table shows the results of a series of patch tests with the sodium soaps on over 300 patients. We have chosen to try to differentiate between mild and definite erythema, since we feel that mild erythema may result from the friction of the cloth square alone and, therefore, should not necessarily be interpreted as a positive reaction to the soap. It is at once evident that among the soaps of the saturated fatty acids, lauric, myristic, palmitic and stearic, the number of significantly positive reactions to patch tests decreases as the molecular weight of the fatty acid increases (lauric to stearic). This cannot be caused by a high  $pH$  of the soaps of low molecular weight, since the  $pH$  of the soap increases with increasing molecular weight of the soap. It is also seen from the table that there are many more positive reactions to patch tests with the soap of unsaturated oleic acid than with the soap of the corresponding saturated stearic acid. Figure 1 shows the results of a series of patch tests with these five soaps (the flexor surface of the forearm has been used in this one test for photographic purposes).

*Reactions to Patch Tests with Sodium Soaps*

Soap	Negative	Mild Erythema	Definite Erythema	Papule	Vesicle	Total
Sodium laurate.....	14	58	128	125	20	343
Sodium myristate.....	40	135	146	6	0	327
Sodium palmitate.....	145	155	40	1	0	341
Sodium stearate.....	288	54	2	0	0	344
Sodium oleate.....	46	108	139	15	0	308

These results confirm the work of Emery and Edwards,<sup>6</sup> who used a different technic for making the patch tests. These results also suggest that even though an olive oil soap (high in sodium oleate) would be less irritating than a coconut oil soap (high in sodium laurate), neither soap would be as nonirritating as one made primarily from sodium palmitate and sodium stearate.

In the second paper<sup>5</sup> of this series, a technic of testing employing a window patch<sup>7</sup> was described for holding a fatty acid in contact with the skin in the presence of buffer solutions of varying  $pH$ . With this same technic, the four saturated fatty acids (lauric, myristic, palmitic and stearic) are held onto the flexor surfaces of the forearms, and the patient is asked to moisten the areas under each patch with a borate-boric acid buffer solution of  $pH$  9 once an hour during the waking hours of a test period of twenty-four hours. The result of the test is read one hour after removal of the patches. The lauric acid usually elicits an intense erythematous or papular reaction, the myristic acid a less intense erythema, the palmitic acid usually a negative reaction but occasionally a

7. Guild, B. T.: Window Patch Test, Arch. Dermat. & Syph. 39:807-810 (May) 1939.

positive reactions to patch tests. Thus, it seemed apparent that if oleic acid could be sulfated so as to convert it almost entirely to the sulfato-octadecanoic acid it would be nonirritating to the skin and possibly would produce a satisfactory detergent when used in conjunction with palmitic and stearic acids.

Such a detergent has now been produced.<sup>8</sup> It contains primarily palmitic, stearic and the sulfato-octadecanoic acids adjusted to a  $p_H$  of 8.5 plus or minus 0.1. It contains no lauric acid and only a small amount of myristic acid (usually less than 5 per cent of the fatty acid fraction). Since the material has received a high sulfation, the amount



Fig. 2.—Reactions to patch tests with lauric, myristic, palmitic and stearic acids in the presence of a buffer solution of  $p_H$  9.

of residual unsulfated oleic acid is negligible. This detergent has been under clinical investigation for the past three years.

Patch tests with a small piece of this detergent on 211 persons elicited 171 negative reactions, 33 reactions of mild erythema, 6 reactions of definite erythema and only 1 papular reaction. The reaction to a patch test with an average toilet soap with this technic is rarely negative; the reaction is usually definite erythema. A patch test with 2 cc. of an 8 per cent solution of this detergent, according to the technic recom-

8. Manufactured under the name "dermolate" by the National Oil Products Co., Harrison, N. J.

DR. JOHN F. MADDEN, Minneapolis: I was surprised at the diagnosis made by Dr. E. T. Bell, chief of the department of pathology of the University of Minnesota. He did not hesitate to say that it was an epithelioma.

**Generalized Progressive Scleroderma.** Presented by DR. FRANCIS W. LYNCH, St. Paul.

Mr. C. O. J., aged 37, had noticed the presence of a large number of wrinkles about the mouth, on the cheeks and on the neck since he had pneumonia, in 1941. His skin was always dry. He had a low basal metabolic rate, for which he had taken 2 grains (0.13 Gm.) of thyroid daily for years. He had one hundred and sixty injections of androgen a year ago because of lack of sexual development following bilateral orchitis in childhood.

There are pallor, dryness and tenseness of the skin in many large, ill defined areas, especially on and near the face. Around the mouth are numerous radial scars. The form of the body is feminine.

**Generalized Progressive Scleroderma.** Presented by DR. JOHN F. MADDEN, Minneapolis.

Mr. E. A. L., aged 48, complained of an eruption most pronounced on the hands, arms, face and feet and present to a less degree on the trunk.

The skin has a hidebound, shiny appearance, with considerable limitation of movements of the fingers. The disease is steadily progressing.

**Generalized Progressive Scleroderma.** Presented by DR. FRANCIS W. LYNCH, St. Paul.

Mrs. C. P. W., aged 36, noted that the skin of the lower extremities had a "tight, drawn feeling," which was more noticeable when she was standing or walking. During several winters she had had a persistent itching eruption. She stated that her feet had been frostbitten on three occasions. The eruption on the thighs did not change after treatment with thyroid, given because of a low basal metabolic rate. The menstrual periods were normal.

The eruption involves the lower extremities, stopping sharply at the iliac folds. The skin is diffusely brown and thickened. On lifting and pressing the skin with the fingers, one notes an appearance of lobulation. The feet are unusually cold.

**Generalized Progressive Scleroderma.** Presented by DR. FRANCIS W. LYNCH, St. Paul.

Miss R. F., aged 26, first noticed an eruption on her wrists in 1939. It gradually extended in spite of numerous therapeutic attempts, including injections of solution of posterior pituitary U. S. P., and later neostigmine methylsulfate, as well as oral administration of neostigmine bromide, thyroid and mecholyl bromide.

There are diffuse tightness and thickening of most of the skin. Roentgenograms show extensive resorption of bone of the terminal phalanges of both hands without involvement of the fourth digit on either hand.

**DISCUSSION ON CASES OF SCLERODERMA**

DR. CARL W. LAYMON, Minneapolis: I thought that this was a most interesting and unusual group of cases. In my opinion, the lesion in the first case (Mr. C. O. J.) did not fit the diagnosis of generalized scleroderma. There was little cutaneous change except in the circumoral region. I wonder whether such cutaneous change could be regarded as of endocrine origin. The fourth case (Miss R. F.) was also unusual in that it presented the rare feature of nodular formation in generalized scleroderma. Several years ago Dr. Michelson had a similar case, which Dr. Butler and I reported in the ARCHIVES.

## POROKERATOSIS

Review and Report of Cases

PHYLLIS E. JONES, M.D.

AND

DUDLEY C. SMITH, M.D.

CHARLOTTESVILLE, VA.

**P**OROKERATOSIS is an unusual chronic progressive keratoatrophoderma, persisting throughout life and characterized by circinate or oval plaques with an annular hyperkeratotic linear elevation at the border, which progresses peripherally leaving a certain amount of atrophy at the center. There is often a dike or slender furrow running along the summit of the border, from which arises a keratotic ridge.<sup>1</sup>

Mibelli, in October 1893, reported 3 cases of a previously undescribed disease which he named porokeratosis after histologic examination, on the ground that the most important anatomic lesion consisted of hyperkeratosis of the sweat duct and sweat pore.<sup>2</sup> One case described by him had been first observed by Majocchi in 1887. The true nature of the disease in this case had not been recognized, and it had been presented as a case of "ichthyosis hystrix." When Mibelli saw the patient he recognized the lesions as exceptional and different from the disease previously recorded. He reported this case along with 2 others, giving a full description of clinical and histologic observations. Three other cases were mentioned, but referred to only briefly.

Mibelli presented his cases as consisting of lesions beginning as minute dry dirty brown warty cone-shaped elevations, less than 1 cm. in diameter, which spread peripherally, leaving a depressed dry callous center. He described the border as having the appearance of a dike, with a shallow central depression at its summit. In 1 instance a lesion reached such a size that the entire forearm and hand were covered. There was a predilection for the hands, face, genitals, legs and feet.

He designated the disease as essentially chronic, beginning in the early years and continuing throughout life. It was unaccompanied with any inflammatory or subjective symptoms. There was mentioned also

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From the Department of Dermatology and Syphilology of the University of Virginia.

1. Becker, W. S., and Obermayer, M. E.: Modern Dermatology and Syphilology, ed. 1, Philadelphia, J. B. Lippincott Company, 1943.

2. Mibelli, cited by Wright.<sup>21</sup>

## LONG HAIR, CHIEF OF THE CROWS

EDWARD F. CORSON, M.D.

PHILADELPHIA

AMONG the races which developed and cultivated long hair in fairly recent times, those of the Mongoloid type, especially the American Indians, were notable, and among these Indians the Crow tribe had the reputation of possessing the most extensive growth. The men outstripped the women in this respect, and pride in their own hirsuties and admiration of this feature in others were to be readily noted in their ingenuous manners.

As background I quote Catlin,<sup>1</sup> who visited the Crows early in the last century and described them as being of fine physique and especially noted for their magnificent growth of hair. He said:

I observed . . . that most of them were over 6 feet [183 cm.] high, and very many of these have cultivated their natural hair to such an almost incredible length, that it sweeps the ground as they walk; there are frequent instances of this kind amongst them, and in some cases, a foot or more of it will drag on the grass as they walk, giving exceeding grace and beauty to their movements. They usually oil their hair with a profusion of bear's grease every morning, which is no doubt one cause of the unusual length to which their hair extends; though it cannot be the sole cause of it, for the other tribes throughout this country use the bear's grease in equal profusion without producing the same results.

The present chief of the Crows, who is called Long Hair and has received his name as well as his office from the circumstances of having the longest hair of any man in the nation, I have not yet seen: . . . This extraordinary man is known to several gentlemen with whom I am acquainted, and particularly to Messrs. Sublette and Campbell . . . who told me they had lived in his hospitable lodg<sup>e</sup> for months together; and assured me that they had measured his hair by a correct means, and found it to be 10 feet and 7 inches [323 cm.] in length; closely inspecting every part of it at the same time, and satisfying themselves that it was the natural growth.

This is nonscientific evidence from members of a class of persons (travelers and traders) who were sometimes inclined to exaggerate. Nevertheless, they were practical, and their inspection and measurement are not far out of line with the statements of some others of that period, the 1830's. It constitutes the first mention, as far as I can

1. Catlin, G.: Letters and Notes on the Manners, Customs and Condition of North American Indians, ed. 3, London, Tilt & Bogue, 1842.

DR. CARL W. LAYMON, Minneapolis: The histologic pictures of kraurosis vulvae and lichen sclerosus et atrophicus are similar. One point of differentiation is the obliteration of the deep blood vessels in kraurosis vulvae. In the present case the histopathologic picture was compatible with the diagnosis of lichen sclerosus et atrophicus.

DR. RUBEN NOMLAND, Iowa City: I do not think one can tell the difference in the two diseases. Atrophic areas in one look like the atrophic areas in the other, and the hypertrophic areas also look alike, but with more change in these areas in kraurosis.

**Periarteritis Nodosa.** Presented by DR. FRANCIS W. LYNCH, St. Paul.

B. L., a woman aged 21, stated that a feeling of exhaustion was present throughout 1944 and became worse after extraction of thirteen teeth in December 1944. Later nervousness was noted and she lost 8 pounds (3.6 Kg.). Chronic bronchitis had been present since March 1945. An eruption appeared on the legs two years prior to examination and followed an irregular course, becoming worse recently. In 1942 she had unilateral facial paralysis, of undetermined origin.

The eruption did not improve with oral administration of benadryl hydrochloride (diphenhydramine hydrochloride) or with sulfadiazine, which was given because of acute bronchitis in November 1945. There was no reaction to intradermal injection of old tuberculin in 1:1,000 dilution. The leukocyte count was 13,400; the sedimentation rate was 18 mm. in one hour. Roentgenogram of the chest showed only increased bronchovascular markings. Serologic reactions were negative for syphilis. Urinalysis revealed a trace of albumin in January and a 3 plus reaction for albumin in October 1945.

On the anterior aspect of each leg and of the knees there are discrete light red, tender, deep papules and small nodules.

Histologic examination revealed a thrombotic vessel with necrotic areas around it.

#### DISCUSSION

DR. HENRY E. MICHELSON, Minneapolis: We should be glad indeed to have the privilege of seeing this patient, because more and more there is an effort to look past the morphologic manifestations in diseases of the nodosum group. Certainly, periarteritis nodosa should be seriously considered when erythematous patches are seen on the legs.

DR. LOUIS A. BRUNSTING, Rochester, Minn.: This woman had treatment with sulfadiazine, without influence on the disease. In some of the reported cases the sulfonamide drugs have been blamed for the production of periarteritis nodosa.

DR. FRANCIS W. LYNCH, St. Paul: This patient was presented with the cooperation of Dr. Arden Miller, who was responsible for her general examination and care. We did not find evidence of allergy or of exposure to known causes of periarteritis nodosa. The sulfadiazine was administered long after the onset of the eruption, without great concern as to possible ill effects. While it has been clearly established that sulfonamide drugs can produce these changes in certain persons, it was thought that such an occurrence must be rare. We have withheld penicillin but have planned to administer it soon after this meeting.

**Benign Familial Pemphigus.** Presented by DR. FRANCIS W. LYNCH, St. Paul.

Mr. H. A. S., aged 41, complained of a slightly itching eruption that had recurred on the sides of his neck for four or five years, especially at the collar line. This eruption followed an irregular course, with improvement in some areas and new appearance in others. The eruption was moist at times. His general health was good. A recurrent eruption on the neck was present in a female cousin on the paternal side.

On each side of the neck, especially on the right, there is a red, slightly moist and crusted eruption with irregular outline.

surface be damaged from any cause acidity may produce itching, which would not occur if the scalp were intact. Itching of the scalp may also occur, of course, dissociated from acidity.

The relation of the acidity of the scalp to the somewhat indefinite disease spoken of as seborrhea is not clear and will require further study. The scalps studied by us were given a careful clinical examination. No definite correlation of dandruff or other symptoms with acidity was noted, indicating that acidity is not the only factor involved. This does not exclude the possibility of acidity's being of importance at certain stages in the development of seborrhea. Because of the definite antibacterial action of such acidity it would be surprising if this were not the case. Further work will, however, be required to determine just what role acidity may play.

#### SUMMARY AND CONCLUSIONS

The human scalp was observed to have a distinctly acid reaction. The acidity usually varied between  $p_H$  4.5 and 5.5. The acidity was due to lactic acid secreted in the sweat and, to a lesser degree, to volatile fatty acids which are believed to be formed from the lactic acid by micro-organisms on the scalp. The acidities observed were adequate to account for a definite antibacterial action for many types of micro-organisms and are believed to be of importance in the prevention of infections of the scalp. The accumulation of acids is believed to be not uncommonly associated with itching of the scalp, which is relieved by washing. Washing reduces the acidity temporarily. No uniform relationship was observed between acidity and seborrhea. Further work will be required to determine just what the role of acidity is in this disease.

## TREATMENT OF PLANTAR WARTS

HARVEY BLANK, M.D.\*

PHILADELPHIA

A HIGHLY successful method of treatment of plantar warts, without complications and without roentgen rays, is presented. Numerous methods of treatment have been proposed, but none has been entirely satisfactory. The method described in this report is simple, requires little equipment, does not disable the patient, cures a high percentage and causes no complications or painful sequelae. It is particularly useful when adequate roentgen ray therapy is not available or has failed to destroy the lesion.

The method used aims to overcome the two main problems of the treatment of plantar verrucae, namely, the inaccessibility of the lesion and the adequate destruction of its substance without producing a painful scar. The verruca is made accessible by applying a thick ring pad around the lesion so that when the patient bears weight on the foot the verruca is extruded through the hole. Adequate destruction of the lesion is accomplished with the proper application of phenol and nitric acid. Either of these drugs used alone may cause destructive changes which are unpredictable and result in injury to the patient. If they are used in combination by first applying phenol and following it immediately with nitric acid, the penetrating necrosing action is controlled by the reaction which converts the two chemicals into trinitrophenol (picric acid). The instantaneous reaction which occurs produces a tiny tough eschar in the tissue which protects the skin from further caustic action and thus gives complete control of the degree of destruction.

It should be emphasized that the chemical cauterization of plantar warts is associated with danger. These substances must be applied carefully in small amounts in order that only the lesion itself be touched and that the surrounding normal skin be undamaged. If used correctly, in accordance with the procedure described, this chemical method is safe.

### METHOD AND MATERIALS

The materials necessary are a scalpel, adhesive plaster, 90 per cent phenol, concentrated nitric acid, 60 per cent salicylic acid ointment and, if possible, a piece of stiff felt.

\* Formerly Major, Medical Corps, Army of the United States.

From the Department of Dermatology and Syphilology, University of Pennsylvania Medical School, Dr. Donald M. Pillsbury, Director.

Examination shows a 4 cm. lesion on the left malar eminence, dark brown to black, superficial and entirely asymptomatic.

#### DISCUSSION

DR. CARL W. LAYMON, Minneapolis: The term junction nevus seems more accurate from the histologic than from the clinical standpoint. Junction nevus presents considerable disruption of the basal layer and numerous epidermal lacunae. There are numerous cells in mitosis. Junction nevi are smooth, usually dark and completely devoid of hair. Lesions which have been called lentigo maligna present the histologic picture of junction nevus.

DR. RUBEN NOMLAND, Iowa City: I have seen a malignant melanoma develop from the senile pigmented lesion in 5 or 6 cases. The dark senile freckles (lentigo maligna) are similar microscopically to junction nevi. Some of the pigmentary changes in senile pigmented lesions are similar to those in xeroderma pigmentosum. Dr. M. J. Reuter, of the Mayo Clinic, reported a case of xeroderma pigmentosum in which this type of pigmentary change was prominent. I believe that senile pigmented lesions often give rise to malignant melanomas and that such lesions are similar microscopically to junction nevi.

A Case for Diagnosis (Pigmented Plaques). Presented by DR. JOHN F. MADDEN, St. Paul.

MR. R. S. P., aged 30, noticed a pigmented, asymptomatic lesion of the left side of the forehead in May 1945. This was about the size of a pea and increased to the size of an olive. New lesions formed, and none of the old ones disappeared. The patient stated that he did not take any internal medication.

Examination reveals lesions on the left temple, the left side of the neck and over the left scapula. They vary in size from 1 to 3 cm. and are dark brown and asymptomatic.

#### DISCUSSION

DR. STEPHAN EPSTEIN, Marshfield, Wis.: I believe this may be a fixed dermatitis medicamentosa. The patient admitted taking "anacin" (a preparation of acetophenetidin with acetylsalicylic acid, caffeine and quinine sulfate) once a month.

DR. RUBEN NOMLAND, Iowa City: My colleagues and I had a patient in the hospital with dermatitis medicamentosa due to phenolphthalein, and we determined that she had a period during which she was refractory to the drug. We gave her phenolphthalein at various intervals after she had had a flare-up. We found by repeated trials that no eruption could be produced until at least seven days after an attack; so we concluded that her refractory period was about a week. The same thing is true of fixed dermatitis medicamentosa due to phenobarbital. We had an opportunity to study a nurse with such an eruption and found that she had a refractory period of probably three to four days' duration.

DR. SOLOMON HORWITZ, Minneapolis: I had a similar experience with a sulfonamide drug. I, too, noticed a refractory period. The patient had several recurrent attacks of gonorrhea, and each time he resumed taking the drug there developed a fixed dermatitis involving the dorsum of the right hand.

DR. STEPHAN EPSTEIN, Marshfield, Wis.: Dr. Nomland's experience of a refractory phase of from five to seven days can well be explained on the basis of exhaustion of antibodies. Fellner (*Dermatologica* 87:81, 1943) demonstrated by *in vitro* experiments that an antigen-antibody reaction actually occurs in these eruptions.

DR. JOHN F. MADDEN, St. Paul: I have never seen a fixed dermatitis medicamentosa that did not show activity after the drug was administered. "Anacin" was given well beyond the limits of a refractory period without change in the eruption. These lesions have never changed from the onset except for enlargement in the circumference.

Since it is important to dermatologists and to physiologists to know just what type of work a normal sweat gland is capable of doing, this investigation of the collection and analysis of sweat was undertaken.

As previously reported,<sup>2</sup> the palmar sweat glands were selected for study since the nature of their physiologic functions and the position of their duct openings made it possible to collect sweat which was free from contamination by surface cells, oils and bacteria. With the chamber specially designed for these studies,<sup>2</sup> it is possible to see the opening of the individual sweat duct during the period of collection, and thus the manner and rate of secretion of sweat can be observed.

For the studies on chloride in sweat reported in this paper the same procedures were followed as described in the preliminary report<sup>2</sup>: sweat was collected from fifty glands for thirty minutes, urine was collected for the same period and a sample of venous blood was drawn at the conclusion of the period. The work was carried out during cool or cold months of the year. An interval of at least two days elapsed between repeated studies on the same person. The volumes of sweat were measured by the manipulative technic of

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- D. B.; Hall, F. G., and Edwards, H. T.: Changes in Composition of Sweat During Acclimatization to Heat, *ibid.* **123**:412-419 (Aug.) 1938. Usher, B.: Human Sweat as a Culture Medium for Bacteria, *Arch. Dermat. & Syph.* **18**:276-280 (Aug.) 1928. Peck, S. M.; Rosenfeld, H.; Leifer, W., and Bierman, W.: Role of Sweat as a Fungicide, with Special Reference to the Use of Constituents of Sweat in the Therapy of Fungous Infections, *ibid.* **39**:126-146 (Jan.) 1939. Favre, A., cited by Way and Memmesheimer. Mosher, H. H.: Simultaneous Study of Constituents of Urine and Perspiration, *J. Biol. Chem.* **99**:781-790 (Feb.) 1933. Mickelsen, O., and Keys, A.: The Composition of Sweat, with Special Reference to the Vitamins, *ibid.* **149**:479-490 (Aug.) 1943. Keutman, E. H.; Bassett, S. H., and Warren, S. L.: Electrolyte Balances During Artificial Fever with Special Reference to Loss Through Skin, *J. Clin. Investigation* **18**:239-250 (March) 1939. Way, S. C., and Memmesheimer, A.: The Sudoriparous Glands: III. Sweat, *Arch. Dermat. & Syph.* **41**:1086-1107 (June) 1940. McCance, R. A.: The Effect of Salt Deficiency in Man on the Volume of the Extracellular Fluids, and on the Composition of Sweat, Saliva, Gastric Juice and Cerebrospinal Fluid, *J. Physiol.* **92**:208-218 (March) 1938. Mezincescu, M.: A Phase of Problem of Acclimatization to High Temperatures, *J. Indust. Hyg. & Toxicol.* **19**:146-151 (March) 1937. Hardt, L. L., and Palmer, A.: Studies in Intermittent Heat Sweats: The Chlorides and Acid-Base Balance, *Am. J. Digest. Dis.* **4**:489-492 (Oct.) 1937. Kuno, Y.: The Physiology of Human Perspiration, London, J. & A. Churchill, Ltd., 1934, chap. 8, pp. 176-177. McSwiney, B. A.: The Composition of Human Perspiration, *Proc. Roy. Soc. Med.* **27**:839-848 (May) 1934. Cohen, E. L.: Generalised Hyperhidrosis, *St. Barth. Hosp. J.* **48**:83-84 (June) 1944.

2. Lobitz, W. C., Jr., and Osterberg, A. E.: Chemistry of Palmar Sweat: Preliminary Report; Apparatus and Technics, *J. Invest. Dermat.* **6**:63-74 (Feb.) 1945.

## COMMENT

Wigoder<sup>6</sup> stated the belief that there is no correlation between different species of animals in regard to their tolerance to exposure of the gonads to roentgen rays. The tolerance of testes of rats, mice, rabbits and guinea pigs roughly approximates the tolerance of human ovaries. It seems possible that human testes might fall into this same range of sensitivity to roentgen ray irradiation.

As a conservative estimate, it has been stated that human ovaries, and perhaps testes, may be directly exposed to as much as 150 r without injury.<sup>2a</sup> Since, according to our studies, only 0.034 r would be expected to reach the gonadal region with each exposure of 100 r to the face, a dosage many times greater than any dosage ever used therapeutically would be required to produce theoretic damage to the gonads, even when the gonadal region is not shielded.

TABLE 3.—*Tolerance of Human Ovaries to Roentgen Rays*

Dosage (r) Producing No Injury (Author) 150 (Westing)	Dosage (r) Producing Temporary Sterility (Authors) 360 to 510 (Westing) (Harris)	Dosage (r) Necessary to Produce Permanent Sterility (Authors) 625 to 720 (Mayer and his associates) (Peck and his associates)
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## SUMMARY

The amount of scattered irradiation which may reach the gonadal region of patients receiving low voltage roentgen ray therapy to the face has been estimated as negligible so far as approaching the dosage which might produce injury to the gonadal tissues is concerned. A method for studying the effects of direct roentgen ray irradiation on the spermatogenesis of rabbits is described. Three hundred to 400 r are necessary to produce a suppression of spermatogenesis, 600 to 650 are necessary to produce a temporary arrest in spermatogenesis, and 950 to 1,500 r are required to produce a permanent arrest of spermatogenesis. Biologic studies demonstrated that rabbits that received 300, 600 or 900 r to the testes successfully impregnated female rabbits three months after irradiation, while rabbits that received 1,200 or 1,500 r were presumed to be sterile as a result of the roentgen ray irradiation. The testes of 2 patients with carcinoma of the prostate gland were given direct roentgen ray irradiation and subsequently were studied histologically after bilateral orchectomy. No apparent arrest of spermatogenesis was produced by 300, 600 or 900 r. of roentgen ray irradiation.

The last five chapters deal with the national campaign to control venereal disease. In penicillin we have, for the first time, a drug with which a patient may be rapidly rendered noninfectious. If this potent agent were coupled with a mass program for case finding, it is entirely possible that in our day we could see syphilis stamped out. The authors point out the necessity for individual cooperation. After all, the success of any plan depends on the infected person's being made aware of his disease and then on convincing him of his need for adequate therapy. ". . . there are laws to compel recalcitrant infected people to submit to treatment or isolation." Many times, however, the use of strong measures defeats the program, for it often frightens patients into self treatment or into seeking the advice of incompetent persons.

In chapter 12 Dr. Vonderlehr and Dr. Heller discuss prophylaxis in its broad sense. They point out that prophylaxis usually suggests the use of a chemical agent designed to destroy the germ or prevent it from reaching the body. Yet in its much more important phase prophylaxis should deal with a long range program of education in the home, in the school and in the church.

This excellent book is well written and free of significant errors. It has an adequate index. It is an honest and factual report of the good and bad aspects of the control of venereal disease. The book is written primarily for the average citizen, on whom, after all, the ultimate success of any program for the control of venereal disease must depend. This book is worth reading and is recommended to the dermatologist, the medical practitioner and the public alike.

**Skin Reactions Caused by Fractions of Oil of Turpentine and Hexanitrodiphenylamine. Experimental Investigations by Means of the Adhesion Chamber Method.** By Ingvald Rokstad. *Acta dermato-venereologica, volumen XXVI, supplementum XV.* Pp. 311, with 27 black and white illustrations. Helsingfors, Finland: Mercatoris Tryckeri, 1946.

This is an extensive monograph dealing with experimentally induced sensitization eczema by way of fractions of oil of turpentine and hexanitrodiphenylamine. Details as to technic and extensive protocols are included. The concluding sections deal with the nature of eczematous sensitization, its localization and its reaction mechanism. Nothing new for American dermatologists is revealed by this study, except perhaps the use of the "adhesion chamber method" of cutaneous testing.

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## News and Comment

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### GENERAL NEWS

**Application for Space in Scientific Exhibit.**—Fellows of the American Academy of Dermatology and Syphilology who wish to apply for space in the Scientific Exhibit at the Chicago meeting of the Academy in December 1947 are requested to write for an application blank to Dr. Marcus R. Caro, 25 East Washington Street, Chicago 2, Illinois.

Because of the patient's toxic state and septic temperature, ranging from 102 to 105 F., her left leg had to be amputated. The stump healed by primary intention, and she was discharged from the hospital. She was readmitted April 28, 1941 because of seropurulent drainage from a subepidermal nodule of the right thigh, from a biopsy of which a diagnosis of mycosis fungoides was made. The nodule was treated with 1,400 r (unfiltered) in split doses, which resulted in resolution and healing. New nodules subsequently appeared and became ulcerated. These nodules also involved the left thigh and the area of the amputation stump, making it impossible for the patient to wear an artificial limb.

She was again readmitted to the dermatologic service on Oct. 16, 1942 because of recurrence of cutaneous ulcers, and on Jan. 20, 1943, there was a sudden elevation of temperature to 104 F. and pain in the right side of the chest, associated with a cough. There were decreased breath sounds and dulness to per-



Fig. 1 (case 1).—Ulcer of the leg in a *d'emblee* form of mycosis fungoides.

cussion in the lower part of the right side of the chest. A roentgenogram showed fluid in the base of the right side of the chest, with congestion and consolidation in that area, and a diagnosis of pneumonia of the lower lobe of the right lung was made. Pneumotyping showed a type XVII pneumococcus. After the administration of sulfathiazole the temperature returned to normal within three days. However, there were daily elevations of temperature to 100 F. A roentgenogram of the chest at this time showed a density in the right cardio-phrenic angle and a rounded mass in the right side of the chest posteriorly. On February 24, a thoracentesis of the right pleural cavity was performed, which showed a cell count of 2,365 white cells per cubic millimeter, with 21 per cent neutrophils and 79 per cent mononuclear cells. Culture of this fluid did not produce organisms. High daily elevations of temperature recurred, and she became critically ill. She died on March 14.

involvement. Werth<sup>18</sup> found 31 instances of pulmonary involvement and added 2 cases of his own. He stated that reports of pulmonic lesions of mycosis fungoides were uncommon because of physicians' failure to obtain roentgenograms of the chest. Werth described the lesion of mycosis fungoides of the chest, as shown roentgenographically, as marble-like but showing the clear apices until late in the disease, which differentiates it from tuberculosis. However, atypical tuberculosis, miliary tuberculosis and miliary lupoid (Boeck's sarcoid) had to be considered and ruled out.



Fig. 3 (case 1).—Section of the ulcer of the leg in figure 1, showing numerous proliferating reticulum cells as well as karyorrhexis and pyknosis of nuclei.  $\times 650$ .

CASE 2.—A. L., a man aged 72 years, was admitted to the Minneapolis General Hospital on Sept. 21, 1943, complaining of itching of the legs and reddened areas on the back, of six months' duration. The itching became so severe that he was unable to sleep. Two months before admission, a "sore" developed on his back, and the sore had increased in size.

18. Werth, J.: Ueber Lungenröntgenbefunde bei Mycosis fungoides, Arch. f. Dermat. u. Syph. **181**:299-314, 1940.

**SECTIONAL**

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John Kiley, President, 94 Park St., Montclair.  
Henry Abel, Secretary, 339 Union Ave., Elizabeth.  
Place: Academy of Medicine of Northern New Jersey, Newark. Time: Third  
Tuesday of March, April, October and December.

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A. H. Lancaster, Secretary, 608 W. Main St., Knoxville 3, Tenn.  
Place: Andrew Johnson Hotel, Knoxville, Tenn. Time: Aug. 31, 1947.

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WINER—MYCOSIS FUNGOIDES

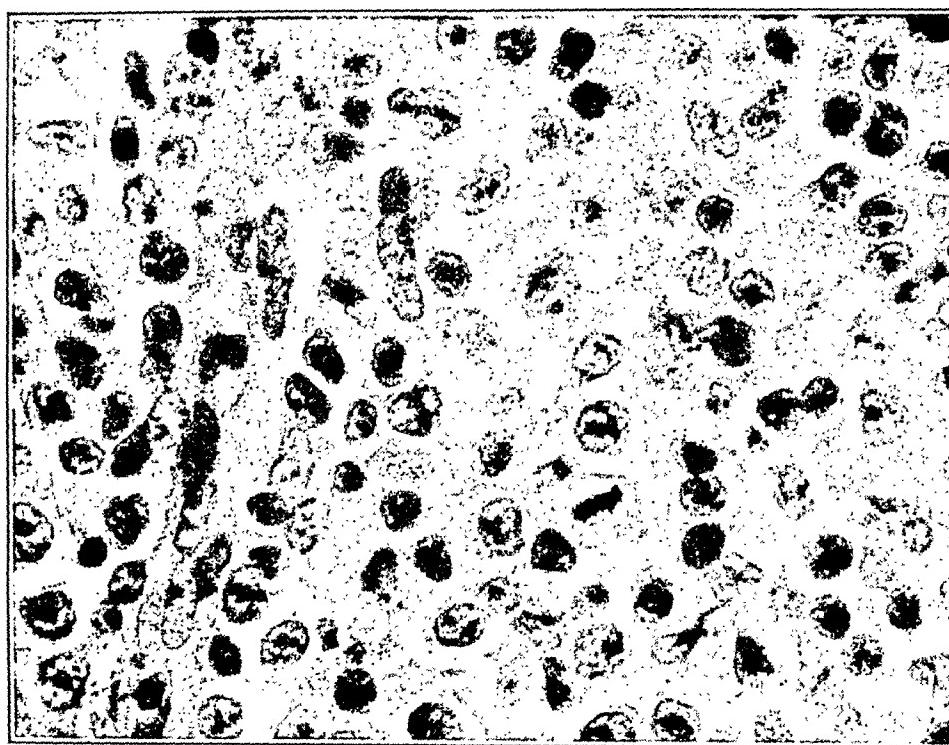


Fig. 5 (case 2).—Lymph node showing two mitotic figures and replacement of normal structure by proliferating reticulum.



Fig. 6 (case 3).—Diffuse alopecia in mycosis fungoides involving the

## CUTANEOUS ERUPTIONS FROM STREPTOMYCIN

MAJOR KARL STEINER  
AND  
LIEUTENANT GEORGE W. FISHBURN  
MEDICAL CORPS, ARMY OF THE UNITED STATES

THE TOXICITY of streptomycin has been discussed in detail by a number of authors. Cutaneous eruptions from streptomycin, however, are mentioned in only two papers. Heilman and his collaborators<sup>1</sup> observed "dermatitis (toxic erythema) and cutaneous eruptions of an urticarial type" and warned, "Although . . . streptomycin may be continued . . . it is exceedingly important to remember that severe dermatitis may result." These remarks were based on the observation of 40 patients. In the report on streptomycin by the National Research Council (Chester S. Keefer, chairman)<sup>2</sup> many more particulars on cutaneous eruptions are given. Forty-nine cutaneous eruptions were observed among 1,000 cases reported. During a period of treatment of ten days the cutaneous lesions appeared in 34 cases on any day from the second on, and especially increased incidence was not noted at any time, unless the 14 eruptions which developed on the fourth or fifth day should be interpreted as higher incidence. In 4 cases the eruptions showed up on the first, second or fifth day after the termination of treatment. In 11 cases the date of appearance of eruptions was not specified. In only 18 of the 49 cutaneous reactions were the durations noted: 8 lasted one day, 1 each seven and nine days, respectively, and 8 for periods of two to five days (3 for two days, 2 for three days, 1 for four days and 2 for five days). Erythematous, urticarial, maculopapular and hemorrhagic reactions, with and without fever, were seen, but there were no rashes of a specific character. Four patients who received a single injection of streptomycin a few weeks after the first series presented recurrences of cutaneous eruptions. In 1 case an injection of 0.0375 Gm. which was given

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From the Dermatological Section and the Tuberculosis Section of Fitzsimmons General Hospital, Denver.

1. Heilman, D. H.; Heilman, F. R.; Hinshaw, H. C.; Nichols, D. R., and Herrell, W. E.: Streptomycin: Absorption, Diffusion, Excretion and Toxicity, Am. J. M. Sc. **210**:576-584 (Nov.) 1945.

2. Keefer, C. S.: Streptomycin in the Treatment of Infections: A Report of One Thousand Cases, J. A. M. A. **132**:70-76 (Sept. 14) 1946.

CLEVELAND DERMATOLOGICAL SOCIETY

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Morris Moore, Secretary-Treasurer, 3427 Washington Blvd., St. Louis 3.  
Place: Barnard Free Skin and Cancer Hospital. Time: 8 p. m., third Monday  
of each month.

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Frances M. Keddie, Secretary-Treasurer, 450 Sutter St., San Francisco.  
Time: Third Friday of February, April, September and November.

hemolytic staphylococci were observed in the urine discharged by catheterization. Because of this infection she received sulfadiazine and later penicillin, after which she had severe urticaria. Since the urinary infection did not clear up, the patient received 1 Gm. of streptomycin a day beginning May 9, 1946, after the urticaria had cleared up. On May 16, seven days after the start of treatment with streptomycin, there appeared a slightly raised erythema on the right forearm, at the site of a Mantoux test done on Jan. 31, 1946 that had elicited a positive reaction of 1 plus. On May 17 the erythema became more pronounced and raised and rather circumscribed. From this erythema an irregular, macular and patchy, bright pink rash was spreading up the entire arm, especially on the flexor surface. On the left arm there was an erythema of the same character but less pronounced. In the course of the day there was further spread of the eruption, until a generalized, severely pruritic urticaria had developed. Streptomycin was discontinued, and the patient received epinephrine. On the next day there was some improvement, and the urticaria subsided gradually until the end of the month. No particular systemic reactions accompanied the cutaneous eruption.

More than a month later, in July, the patient received another course of streptomycin for ten days, and she again experienced a rash, this time after three days, that lasted eight to ten days. Again there were no other systemic reactions. A repetition of the treatment with penicillin did not cause another cutaneous eruption.

#### COMMENT

As compared with the observations of the National Research Council<sup>2</sup> this report necessarily suffers from the error of the small number of cases which were studied. Furthermore, confirmation on the basis of much more material is required to verify the following conclusions. This paper is, therefore, in the nature of a preliminary report to stimulate further investigations.

It seems that the number of cutaneous eruptions from streptomycin can be much greater than was reported by the National Research Council. Six rashes in 33 cases (18.2 per cent) occurred in our series as compared with only 49 in 1,000 cases of the Council (4.9 per cent). It cannot be said whether this was due to a different selection of the cases or to the employment of another brand of streptomycin, but the difference appears to be too great to be accidental only.

In 6 of the 7 reported cases the eruptions appeared on the seventh, eighth or ninth day after the initiation of treatment. This is in striking contrast with the observations of the National Research Council. When considering this fact we could not fail to think of the "erythema of the ninth day" as described by Milian and explained by him on the basis of "biotropism." Whether this interpretation applies to the eruptions from streptomycin is as yet impossible to say. The eosinophilia, which was frequently considerable, certainly points to an allergic mechanism in the development of the rashes, as does the "accelerated reaction time" on readministration of streptomycin, which was observed by the investigators of the Council as well as by us. It seems safe to say that the eruptions from streptomycin are not of a toxic but of an allergic nature.

## DISSEMINATED ULCERATING SPOROTRICHOSIS WITH WIDESPREAD VISCERAL INVOLVEMENT

Report of a Case

WILLIAM T. COLLINS, M.D.  
CINCINNATI

A REVIEW of the American literature on sporotrichosis has revealed few cases with visceral involvement. The present report is of a case in which there were widespread visceral lesions.

The number of cases of sporotrichosis reported in this country now total over 200, the majority being from the Mississippi Valley region. The organism is widely distributed as a saprophyte on vegetation, and Foerster<sup>1</sup> has emphasized the occupational hazard of sporotrichosis among farmers and horticulturists and the importance of the barberry shrub as a source of infection.

Sporotrichosis is a disease with several clinical types, which are usually classified as follows:

1. Localized type: This is the commonest form in the United States. A primary ulcerated lesion, or chancre, appears usually on the hands or forearms and is followed after several days by the development of circumscribed hard painless subcutaneous nodules, which frequently ulcerate, along the course of the regional lymphatic vessels.
2. Disseminated gummatoous type: This variety is more frequently encountered in France and is manifested by widely scattered hard painless subcutaneous nodules that soften and form abscesses, but rarely ulcerate unless traumatized.
3. Disseminated ulcerative type: This form is similar to the preceding type but is characterized by early spontaneous ulceration, producing lesions which resemble the ulcerative lesions of tuberculosis and tertiary syphilis.
4. Extradermal type: The mucous membranes, the muscles, the bones and joints, the eyes and rarely the viscera may be invaded by the organism.

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From the Departments of Dermatology, Bacteriology and Pathology, Cincinnati General Hospital.

1. Foerster, H. R.: Sporotrichosis: Occupational Dermatoses, J. A. M. A. 87:1605-1608 (Nov. 13) 1926.

The following steps were taken: 1. Dichloroacetic acid was applied to the portion of the mass covered with skin. Whitening of the skin indicated adequate penetration of the keratin, which is a barrier to the passage of zinc chloride. 2. Zinc chloride fixative paste<sup>6</sup> was applied in a depth of about 2 mm. 3. The treated area was covered with cotton and then with an overlapping cotton dressing spread with petrolatum to make a moisture-tight closure. 4. On the next day part of the cancer was excised (first excision, fig. 2A). The incision was made through the deeper portion of the fixed tissue but not through living tissue, so that no pain or bleeding was caused by this operation. The cancer at this level was grossly visible as white crumbly tissue, so the fixative was reapplied in a depth of approximately 0.5 mm. 5. The next day a second layer of tissue was excised. Since

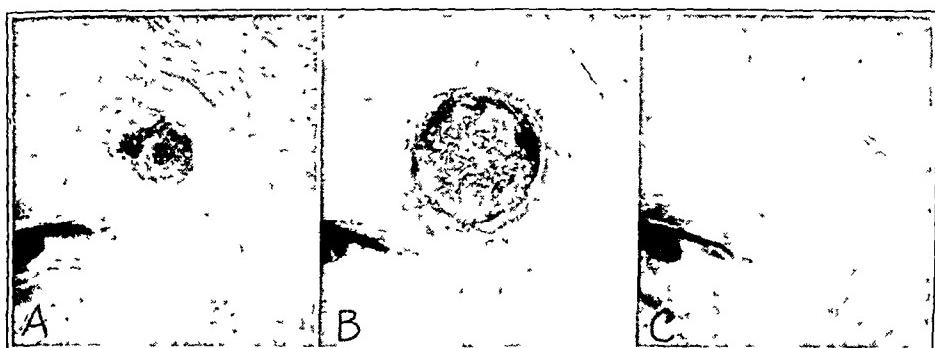


Fig. 1.—*A*, squamous cell epithelioma. *B*, granulation tissue ten days later, after the cancer had been excised in three stages (see fig. 2) and after the final layer of fixed tissue had separated. *C*, healed lesion. The patient was free of cancer when she died of other causes after eight years.

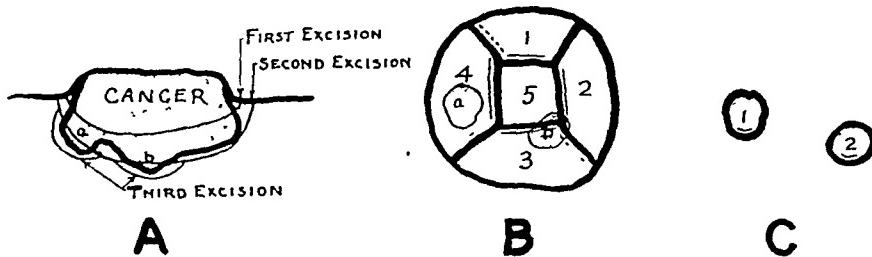


Fig. 2.—Diagram illustrating the chemosurgical technic as used in the treatment of the lesion pictured in figure 1. *A*, vertical cross sectional view showing the levels of the three excisions and the position of the two outgrowths, *a* and *b*, from the main cancerous mass. *B*, map of the five specimens which comprised the second excised layer. Microscopic examination of the frozen sections cut through the under surface of each of these specimens revealed cancer in the stippled areas. These areas of cancer corresponded to downgrowths *a* and *b* in *A*. *C*, map of the specimens from the third excision. Cancer was not present.

cancerous tissue was not grossly visible at this level, the excised layer was divided into five specimens of convenient size (fig. 2B), their edges were marked with merbromin (solid lines) and ordinary bluing (dotted lines) for orientation, and

6. The zinc chloride fixative paste contains 40 Gm. of stibnite (80 mesh sieve), 10 Gm. of powdered sanguinaria and 34.5 cc. of a saturated solution of zinc chloride

Two more cases of pulmonary sporotrichosis were reported by Singer<sup>8</sup> in 1928. In one, the diagnosis was based on the presence of miliary nodules in roentgenogram of the chest, pleural effusion, negative reactions in sputum tests for tubercle bacilli, Sporotrichum in pus aspirated from subcutaneous abscesses and improvement in the cutaneous and pulmonary lesions following potassium iodide therapy. In the other case, the evidence consisted of a proved cutaneous infection by Sporotrichum, an empyema of the pleural cavity, which communicated with a subcutaneous abscess, and improvement following the use of potassium iodide. Considerable doubt is cast on the diagnosis in the second case by the discovery of tubercle bacilli in the empyema fluid, but Singer expressed the opinion that both diseases were present in the lung.

In 1935, Moore and Kile<sup>9</sup> reported a case of generalized cutaneous sporotrichosis with roentgenologic evidence of extensive infiltration of both lungs, which decreased greatly after medication with potassium iodide.

#### REPORT OF A CASE

*History.*—A 67 year old white man was admitted to the Cincinnati General Hospital on Sept. 26, 1945. The patient's past history and family history were irrelevant. He had been the manager of a local theater for seventeen years, but had been retired for the past few years.

Two months before admission the patient experienced pain and swelling in the left knee, which gradually disappeared after medication with "pills and liquid medicine" for a period of one to two weeks. Three weeks before admission numerous small red papules appeared on his arms and then slowly increased in number to cover the entire body, including the face. The papules rapidly enlarged, and many developed into ulcers. The patient was entirely asymptomatic, aside from the presence of the lesions.

*Physical Examination.*—The patient was well nourished and did not appear acutely ill. Numerous lesions, varying from small erythematous papules to large blood-crusted ulcers, were present on the trunk, face and extremities. The superficial lymph nodes were not enlarged. Resonance and breathing sounds were normal over both pulmonary fields. The edges of the liver and spleen were palpable 3 and 4 fingerbreadths, respectively, below the costal margins, but were smooth and not tender.

*Laboratory Data.*—The blood and urine were normal, as shown in analyses, throughout the course of hospitalization. Reaction to Wassermann and tuberculin tests (purified protein derivative numbers 1 and 2) were negative. Examination of the sputum revealed no acid-fast bacilli. The level of serum protein was 5.74 Gm. per hundred cubic centimeters. The spinal fluid contained 37 mg. of protein per hundred cubic centimeters and 20 white blood cells per cubic millimeter, but no organisms were observed and the fluid was not cultured. *Staphylococcus aureus* was isolated from cultures of the cutaneous lesions. A roentgenogram of the chest

8. Singer, J. J.: Am. Rev. Tuberc. 18:438, 1928.

9. Moore, M., and Kile, R. L.: Generalized, Subcutaneous Gummatous Ulcerating Sporotrichosis, Arch. Dermat. & Syph. 31:672-685 (May) 1935.

## BLASTOMYCO<sub>SS</sub>, NORTH AMERICAN TYPE

A Proved Case from the European Continent

MELVIN BRODY, M.D.  
CLEVELAND

NORTH AMERICAN blastomycosis is a disease almost exclusively limited to the United States. Martin and Smith,<sup>1</sup> in their exhaustive review of the literature, read of only 2 proved cases reported outside the United States, 1 in Canada and 1 in England. The foreign literature contains many reports of blastomycosis of the Gilchrist or North American type, but the diseases are described and diagnosed so inadequately that they cannot be definitely accepted as the Gilchrist type.<sup>2</sup> For example, in no foreign cases are differential cultures described. It is therefore of interest to report the first proved case of North American blastomycosis from the European Continent.

### REPORT OF A CASE

A 24 year old man was inducted into the Army in December 1942. He felt well at that time. In December 1943 he was sent to England, where he remained for nine months. He was then sent to France, and he performed full duty from September 1944 to July 1945, when he first became ill. He experienced symptoms of atypical pneumonia, associated with fever, night sweats, hemoptysis and pain in the right side of the chest. A roentgenogram of the chest revealed a large area of consolidation in the medial portion of the upper lobe of the right lung. The results of repeated examinations of sputum for acid-fast bacilli were negative. The patient was evacuated to the United States and arrived at Kennedy General Hospital on August 22. At that time, in addition to his pulmonary disease, the patient presented cutaneous lesions on the right side of the nose and on the right eyebrow, which had appeared six weeks previously while he was in France. He also had a red tender subcutaneous swelling in the region of the medial malleolus of the left leg of three weeks' duration. The facial lesions were crusted, elevated and papulopustular, with heaped-up margins. The subcutaneous lesion on the left ankle was incised, and bloody necrotic material was evacuated. Cultures from the abscess and from the facial lesions showed typical *Blastomyces dermatitidis*. On histologic examination the lesion on the nose was described as ". . . hypertrophy of the epidermis with a diffuse inflammatory reaction in the cutis. There were

1. Martin, D. S., and Smith, D. T.: Blastomycosis (American Blastomycosis, Gilchrist's Disease): I. Review of the Literature, Am. Rev. Tuberc. 39:275-304 (March) 1939.

2. Conant, N. F., and others: Manual of Clinical Mycology, National Research Council, Division of Medical Sciences, Philadelphia, W. B. Saunders Company, 1944, p. 25.

Thus, a considerable amount of tissue from the frontal lobe may be removed without ill effects, but great care must be exercised to avoid entrance into the anterior horns of the lateral ventricles. The rapid penetration of the fixative through tissue of the brain necessitates the reduction of the amount of fixative applied. Fixed cerebral tissue separates in about seven days and granulation tissue forms, providing a base for rapid epithelialization.

While hemorrhage ordinarily is not a problem, precautions are indicated when the cancer involves regions containing large vessels. Vessels such as the external maxillary and the superficial temporal arteries may require the placement of suture ligature in the wound. If the carotid arteries are thought to be involved, a ligature at a level below the wound is placed before chemosurgical treatment is begun.

Involvement of the temporomandibular joint by deep-seated carcinoma may necessitate destruction of that structure. Ankylosis has not ensued in any case of this type in which the chemosurgical technic was used. However, some degree of malocclusion may occur.

Deep cancerous invasion in the path of the seventh cranial nerve may necessitate interruption of the nerve during chemosurgical excision. However, the conservatism made feasible by the method makes possible the preservation of a maximum amount of nerve tissue. In some cases in which a relatively small segment of a nerve has been interrupted during chemosurgical treatment, there has been a return of function after a year or so.

#### THERAPEUTIC RESULTS IN CASES OF BASAL CELL EPITHELIOMA OF THE FACE

Two hundred and thirty-two basal cell epitheliomas of the face were chemosurgically treated during the seven and one-half years ending Jan. 27, 1944, which date is three years prior to this writing. The cancers were in all stages from early to far advanced. Over a third of the patients previously had been unsuccessfully treated by operation or irradiation. There were no metastases.

*End Results After Three Years or More.*—The 232 cases observed for three years or more were divided into "indeterminate" and "determinate" groups according to the plan of Martin, MacComb and Blady.<sup>7</sup> The indeterminate group included the cases of 49 patients who died of intercurrent disease before the expiration of the three year period without evidence of cancer and the cases of 9 patients who were lost from observation without evidence of cancer when last seen. The determinate group included the unsuccessful results, of which there were none, and the 174 successful results.

7. Martin, H. E.; MacComb, W. S., and Blady, J. V.: Cancer of the Lip, Ann. Surg. **114**:341 (Sept.) 1941.



Fig. 1.—Verrucous sporotrichotic dermatitis.

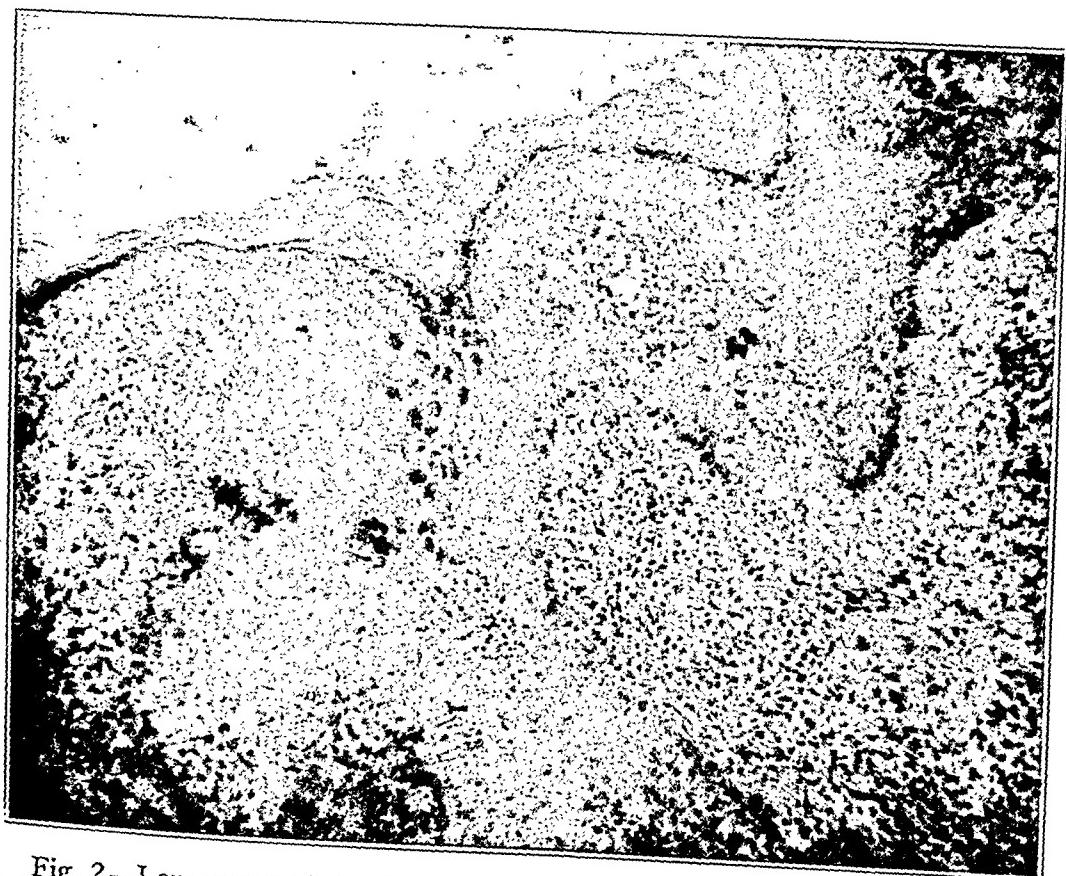


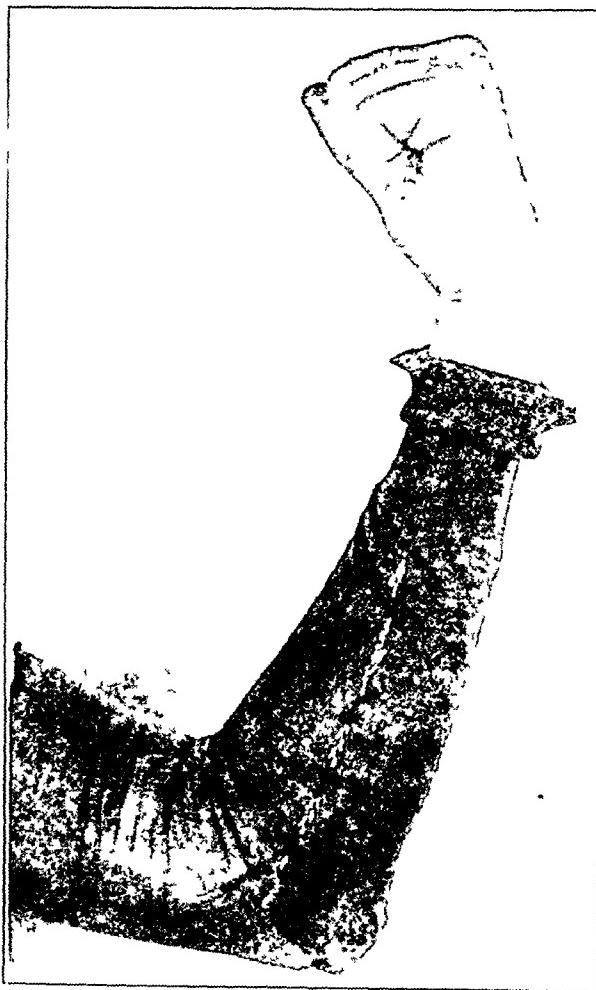
Fig. 2.—Low power photomicrograph showing irregular acanthosis and cellular infiltration in the corium.

## USE OF A SOCK AS AN ELBOW DRESSING

EDWARD F. CORSON, M.D.  
PHILADELPHIA

In these days of scarcity of clothing the following suggestion may be received with reproach, but with appropriately worn-out cotton socks, which are of little value and with the principal holes in the toe, the procedure is not too wasteful and the method rather ingenious and useful. It was brought to my attention by a patient with psoriasis principally affecting the elbows. I have used it in a number of instances.

The region of the elbow is not easily bandaged by persons who do not have training in the art, and the usually tapered forearm encourages a poorly applied



Sock dressing.

dressing to slip down. This permits soilage of the clothing by secretions or "dirty" applications. If, however, a sock is drawn up the arm, in reverse to the usual fashion, through an opening formed by cutting off the toe end, and the foot of the sock is pulled above the elbow so that the heel of the sock receives the point of the elbow, it tends to stay in that position. A dressing of gauze pads, lint or cotton will be held snugly in place without rolled bandage or adhesive fastening. With a small amount of practice the patient becomes skilful at rolling the sock down part way, changing dressings and replacing the cover. For psoriasis of the region of the elbow, pyodermas, dermatitis, decubitus or irritation of the part by bed linen, as frequently noted in bed patients, the sock dressing has given satisfaction

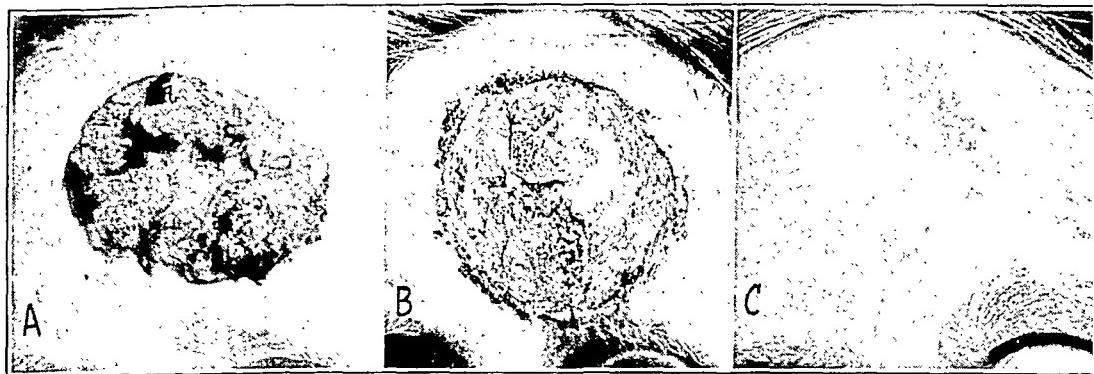


Fig. 5.—*A*, basal cell epithelioma of group D. *B*, granulation tissue and area of exposed skull after removal of final layer of fixed tissue. The layer of fixed bone was removed eleven days later. *C*, healed lesion. The patient was free of cancer when she died of other causes after over three years.

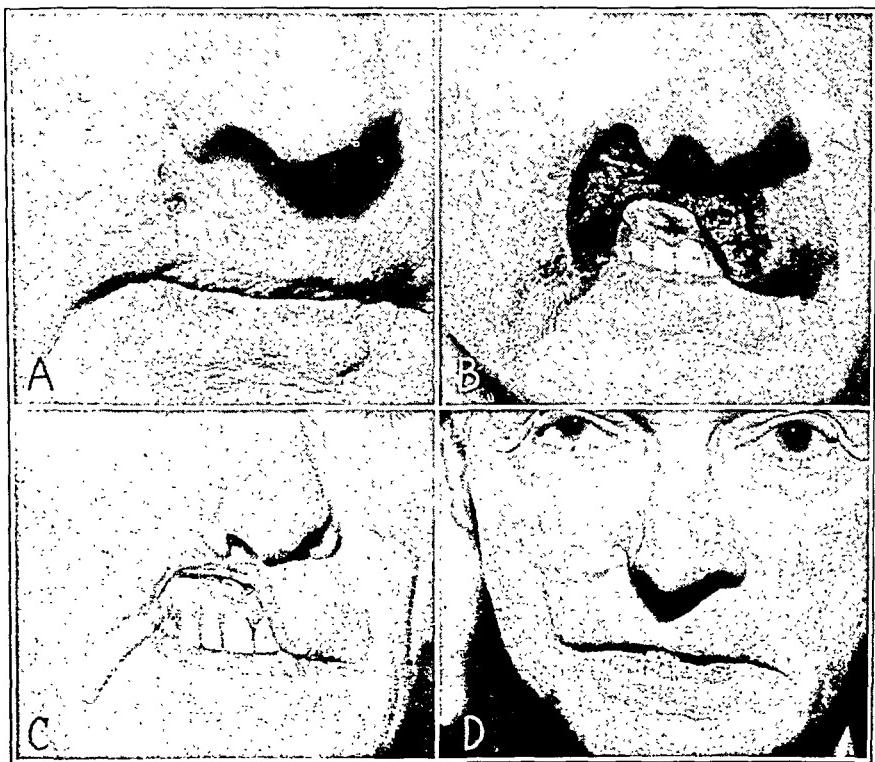


Fig. 6.—*A*, basal cell epithelioma of group C which had recurred after caustic and roentgen ray treatment. *B*, granulation tissue and defect after chemosurgical removal of the cancer in seven microscopically controlled stages. The neoplasm involved much more tissue than the original appearance would indicate. *C*, defect after healing. *D*, appearance after plastic repair by Dr. V. B. Hyslop. The patient is free of cancer after five years.

though they might be surrounding, concentrically, certain spaces which occupied the general osteoid matrix. The structure of genuine bone marrow was not identifiable within these spaces. At most, they contained only a few dilated blood vessels together with fatty areolar tissue. Inasmuch as marrow tissue did not occupy the spaces mentioned and calcification was developed so poorly, it could be stated only that this tissue was osteoid. Such tissue can occur as an expression of metaplasia of bone within old cicatrices or other residua of ancient processes. These observations agree with the circumstances reported clinically."

A case similar to this one has been reported by J. G. Hopkins.<sup>1</sup>

140 East Fifty-Fourth Street.

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1. Hopkins, J. G.: Multiple Miliary Osteomas of Face, *Arch. Dermat. & Syph.* **18**:706 (Nov.) 1928.
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#### SMALLPOX VACCINATION IN RELATION TO VIRUS DISEASE

HERMAN SHARLIT, M.D.  
NEW YORK

A physician has had recurrent herpes simplex for nineteen years. For the first twelve years it was localized to the shaft of the penis; for the last seven, to the right buttock. The attacks never occurred more often than two or three times a year. The last attack subsided April 5, 1947. On April 13 this physician began vaccinating patients. (The Department of Health of New York City recommended that all the population receive cowpox vaccination at once.) Four days later this physician had another attack of herpes on the same buttock, this lesion being about 1 inch (2.5 cm.) from the location of the last. The physician himself had not been vaccinated at this time.

It is impossible for one giving many vaccinations to avoid receiving some of the vaccine lymph on his fingers, without local reaction. It is statistically reasonable, in view of this nineteen year history, to believe that the recurrence of these two attacks of herpes in quick succession was not a coincidence. One may accept the exposure to vaccine lymph as causally related to the last attack.

I need not indulge in obvious comment in this communication, but I would call attention to the opportunity now offered the physicians of New York city to make many helpful observations on the clinical influences of cowpox vaccination on patients with chronic virus infections.

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Observation from the New York Vaccination Campaign.

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#### COMEDOS FOLLOWING ROENTGEN RAY THERAPY

SAMUEL M. BLUEFARB, M.D.  
CHICAGO

The appearance of comedos in a zone surrounding the scar following roentgen therapy for an epithelioma of the face has recently been observed. The case is the first to be encountered out of several hundred cases of epithelioma treated by a similar technic in the dermatology clinic.

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From the Department of Dermatology, Northwestern University Medical School, Edward A. Oliver, M.D., Chairman.

*Examination.*—The girl was normally built and developed. No abnormalities were found except for the scalp and the presence of keratosis pilaris of both arms and thighs.

The temporal, frontal and vertex areas of the scalp were mainly involved. The hair in these regions was short and lusterless and clung closely to the scalp. Throughout the affected areas there were small patches of partial alopecia. The back of the head was not affected, the hair being long and wavy. This hair was combed up over the top as a covering for the involved areas. The length of the diseased hairs varied from  $\frac{1}{4}$  to  $\frac{1}{2}$  inch (0.64 to 1.27 cm.), and the hair was decidedly curled and twisted.

Microscopic examination proved the diseased hairs to be twisted on the long axis of the shaft at regular intervals, the hair shaft between the twists being normal in appearance. The superficial resemblance to monilethrix was striking, but on close examination it was seen that at the constricted points the hair was twisted completely on its axis.

*Treatment.*—Because of the presence of keratosis pilaris and the known influence of large doses of vitamin A on it, she was given 200,000 U. S. P. units of this vitamin daily. At the end of three months the improvement was striking. The keratosis pilaris had completely cleared up, and the alopecia had greatly improved. There was a regrowth of new hair, and the affected hair grew out longer, so that the average length of the hair in the area most involved now measured  $2\frac{1}{2}$  to 3 inches (6 to 7.6 cm.).

#### SUMMARY

A case of pili torti is reported. The disease, from all available evidence of the history, started after a severe attack of scarlet fever. Treatment by high doses of vitamin A was found to be effective for this rare anomaly of the hair.

152 East One Hundred and Seventy-Ninth Street.

Of the 174 basal cell epitheliomas in this series, 112 lesions were predominantly of the invasive type (64.3 per cent). A considerable portion of the invasive lesions exhibited some degree of keratinization (24.3 per cent as compared with 2.8 per cent for the noninvasive lesions). Three of the basal cell epitheliomas contained pigment, and 5 had an adenoid cystic structure.

With the usual surgical treatments or treatments by irradiation the invasive type of epithelioma has a distinctly less favorable prognosis than has the noninvasive type largely because of the presence of unsuspected deep extensions. However, by virtue of the microscopic control of the chemosurgical method all the invasive as well as the noninvasive neoplasms in this series were successfully treated.

*Effect of Site of Cancer on Prognosis.*—All the basal cell epitheliomas in this series were successfully treated regardless of the site of origin. The number of lesions which arose in each site is given in table 3.

TABLE 3.—*Distribution According to Site of Origin of Basal Cell Epithelioma*

Site	Number of Lesions
Cheek.....	65
Temple.....	31
Forehead.....	21
Upper lip (skin).....	18
Neck.....	18
Chin.....	14
Scalp.....	7
All sites.....	<u>174</u>

While these data do not indicate any effect of the site on prognosis, it is obvious that advanced epitheliomas over vital structures, such as the brain or the large vessels of the neck, would have poorer prognoses than would similar lesions in other sites.

#### THERAPEUTIC RESULTS IN CASES OF SQUAMOUS CELL EPITHELIOMA OF THE FACE

A total of 103 squamous cell epitheliomas of the face were chemosurgically treated during the period of seven and one-half years ending Jan. 28, 1944, which date is three years prior to this writing. The cancers were in all stages from early to far advanced, and 27.1 per cent were recurrent after previous treatment elsewhere. Metastases were present in 11.4 per cent of the cases.

*End Results After Three Years or More.*—The 103 cases of squamous cell epithelioma observed for a period of three years or more included 33 in the indeterminate group and 70 in the determinate group. Successful results were obtained in 84.3 per cent of the cases in the determinate group.

DR. EUGENE T. BERNSTEIN: I presented before this society a case of generalized scleroderma in which excellent subsidence of all sclerodermatous features was obtained under treatment with dihydrotachysterol. I also presented a case before the clinic at Mount Sinai Hospital, a report of which was published in *The Journal of the American Medical Association* (140:570 [March 2] 1946). Dr. Wise, in his discussion, stated that this was the first case he had seen in which dihydrotachysterol was efficacious to such an extent, with complete recession of all symptoms.

DR. FRANK VERO: It is unusual to see such extensive changes involving the feet and toes. In a large series of cases at the Presbyterian Hospital, I do not recall one in which there were such pronounced changes on the feet, although one may see hidebound skin on the legs and ankles. This patient presents typical acrosclerosis of the feet, but I am not certain that the lesions on the thighs are morphea unless they are in the stage of involution. I palpated several lesions and could not feel the typical hardness. As to therapy, I have to disagree with the good results from use of the drug (dihydrotachysterol) mentioned by Dr. Bernstein. I have seen a number of patients with scleroderma treated with dihydrotachysterol with no improvement whatever. Dr. Peck is correct as to the difficulty of evaluating any therapy for scleroderma. I have observed several patients who have benefited greatly from a change to a warm climate. Two patients, 1 with diffuse and 1 with progressive scleroderma, went to Florida during the winter and returned with no progression of the disease whatever. I think that massage, diathermy and possibly neostigmine will be of aid in Dr. Silverberg's case. I have obtained good results in some cases from injections of neostigmine methylsulfate and from oral administration of neostigmine bromide.

DR. FRED WISE: Dr. Peck's point is well taken; dermatomyositis, which is probably an infectious disease, is frequently associated with scleroderma-like changes, and it is possible that penicillin might be operative in combating the assumed infectious agent and might also benefit the associated scleroderma.

DR. E. W. ABRAMOWITZ: This patient has atrophy of the skin; the venules are prominent, and, although there is no terminal distal ulceration, ulcerations are present on the heels. He probably has some degree of peripheral vascular disease. He has scattered macular atrophic patches on the legs. In addition, there is a calcareous synovial ganglion on the wrist, and he has acne varioliformis on the scalp. I think the diagnosis of scleroderma should be held in abeyance. In the meantime, baking and massage with oral administration of neostigmine bromide (15 mg. three times a day) might be tried.

DR. MABEL SILVERBERG: Unlike the other patient, I have seen this patient only once.

#### A Case for Diagnosis (Melanoderma?). Presented by DR. FREDERICK REISS.

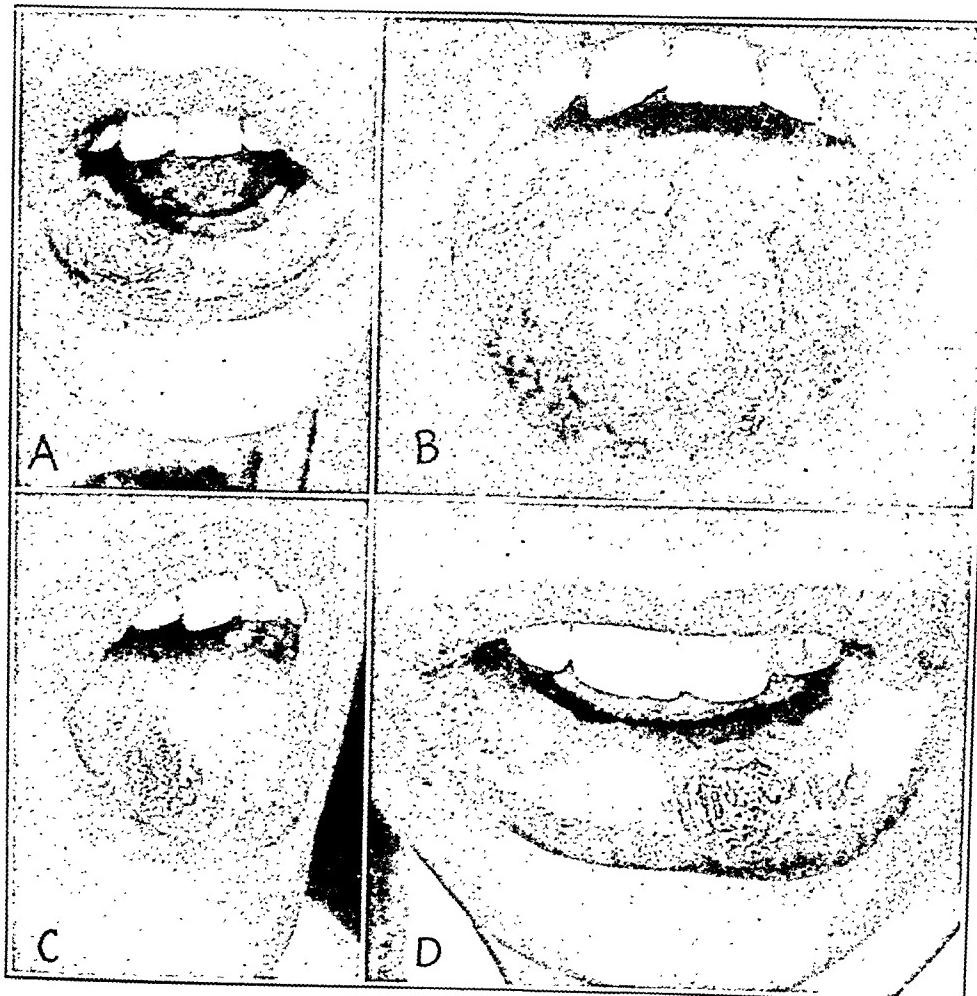
M. J., a Negro woman aged 38, was first observed in the dermatologic clinic, New York Hospital on Sept. 27, 1945, complaining of an eruption on the face of one year's duration. Small lesions, about 1 cm. in diameter, appeared on both cheeks. At the onset these were slightly itchy, dusky gray and nonscaling. At times they became reddish, and small "pimples and blisters" appeared and disappeared as the eruption spread.

On both cheeks and on the forehead there are several hyperkeratotic follicles, which become slightly confluent, forming small, discrete patches, which are partly reticular. Some of the papules have a violaceous color. There is no atrophy.

Granuloma Inguinale Involving the Corner of the Mouth. Syphilis.  
Presented by DR. GEORGE SCHWARTZ, Malden, Mass.

Ulcers of the Mouth ("Periadenitis Mucosa Necrotica Recurrents" or "Ulcus Necroticum Mucosae Oris"). Presented by DR. FRANCESCO RONCHESE, Providence, R. I.

A. D., a white woman aged 32, is presented with lesions at the mouth which had frequently recurred over a period of twenty-five years. The mucous membranes of the mouth, tongue and lips have all been affected. A fresh crop of



Various appearances and locations of recurring aphthous lesions during one year's observation in a 32 year old woman suffering attacks every one to three months for the last twenty-five years. Periods of freedom vary from one to three weeks. Lesions are fungating and almost resemble epitheliomas. Scarring following the repeated deep destruction of tissue over a period of years is evident.

lesions appears every one to three months, lasting several weeks each time. She may be free from lesions for as little as one week between outbreaks. The attacks come on rather suddenly, within a period of only a few hours.

There may be seen numerous deep ulcerations over the dorsum and sides of the distal third of the tongue, on the anterior halves of the buccal mucous membranes, in the gingival fossae and on the labial mucous membranes. These lesions are painful, and some of them are covered with a rather tenacious gray pseudo-

cured. Therefore it is concluded that the prognosis is excellent in squamous cell epithelioma of the face, unless the diameter of the lesion exceeds 3 cm.

The complications which accounted for the poorer prognosis associated with lesions in group D were uncontrolled regional lymph node metastasis in 9 cases, excessive involvement of soft tissues and bone of the temporal region in 1 case and excessive involvement of chin, mandible

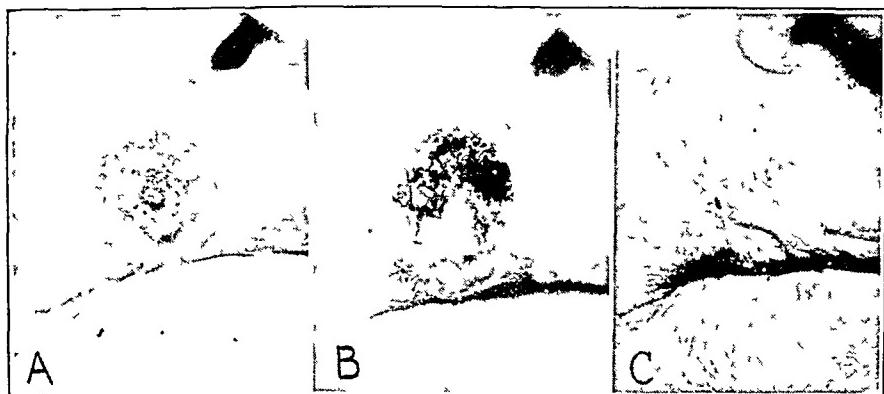


Fig. 8.—*A*, squamous cell epithelioma of group B. *B*, granulation tissue after separation of final layer of fixed tissue. *C*, healed lesion. The patient was free of cancer when he died of other causes after three years.

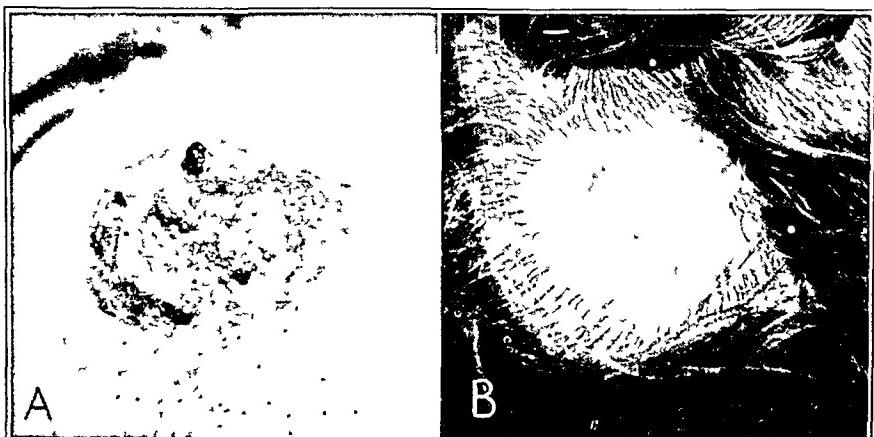


Fig. 9.—*A*, squamous cell epithelioma of group D. The lesion arose in a sebaceous cyst on the scalp. It had recurred after caustic treatments. *B*, healed lesion. The patient is free of cancer after six and one-half years.

and larynx in 1 case. Accordingly, it may be concluded that when a squamous cell epithelioma exceeds 3 cm. in diameter the prognosis becomes poorer because of the increased likelihood of metastasis, the greater chance of the involvement of vital structures and the greater possibility of such extensive involvement of structures of the head and neck that complete removal is impractical.

granuloma inguinale, nor is mention made of other uncommon diseases, such as blastomycosis or allied diseases, which have rather specific histologic pictures, especially when the organisms can be demonstrated.

In the section on nevi there is a disproportionate number of illustrations of nevus sebaceus, and in the description of nevus cells there is no mention of *lames foliacées*, neuroid tubes or clear cells (cellules claires), even though they occur in a relatively small percentage of pigmented nevi. Figures 223 and 224, labeled a case of "nevus pigmentosus (melanoma)," show predominantly the features of verruca senilis (seborrheic keratosis, or what the authors refer to as "nevus senilis" or "seborrheic wart"). Judging from their third picture of this case, figure 225, there apparently were a few ordinary nevus cells, so that both diseases apparently were present. It is difficult to follow the author's concept that angioma serpiginosum is merely a variant of capillary angioma, nor do their illustrations, figures 286 and 287, fit well with the original or subsequent histologic descriptions of this disorder.

The authors state that the atlas is intended primarily for postgraduate students and those interested in special study of dermatology. Because of the briefness of the text and its variance from that of standard texts in terminology, on dermatology and on dermatohistopathology, the book cannot be recommended for undergraduate students. Despite the criticisms that have been made, the book is a valuable addition to the library of pathologists, including especially dermatohistopathologists, and should prove extremely useful and valuable to students of dermatohistopathology, provided, as the authors suggest, that they use the atlas in conjunction with standard texts. The colored photomicrographs alone are worth the price of the book. The book is outstanding and unique in that it is the first atlas on dermatohistopathology, let alone general histopathology, in which all illustrations have been limited to excellent photomicrographs in color. It is hoped that when the next edition comes out further illustrations of other dermatoses will be added and the text amplified and in certain places modified or corrected.

**Penicillin in Syphilis.** By Joseph Earle Moore, M.D. Price, \$5. Pp. 284, with 58 illustrations and 52 tables. Springfield, Ill.: Charles C Thomas, Publisher, 1946.

Here is a timely and valuable book which should serve as a guide for penicillin therapy for all forms of syphilis. With penicillin gaining widespread usage it is fortunate that this monograph should appear to serve as a text for the proper mode of administration of penicillin and, what is more important, as a warning against errors in penicillin therapy.

Admittedly, no person or single group has had sufficient experience or time to gather adequate data on this vast subject. With that fact in mind, Moore has pooled the results of nationwide studies by forty-four groups and clinics, drawing from twenty-six civilian institutions as well as the medical services of the United States Army, Navy and Public Health Service rapid treatment centers.

This well organized book is divided into nineteen chapters, the first eight of which deal with the chemistry, pharmacology, toxicity and mechanism of action of penicillin. The reviewer feels that chapter 5 could have been shortened by deletion of material which is not pertinent to the subject. Some fifteen pages deal with the effect of penicillin on various organisms and the results obtained in the treatment of pneumococcic, streptococcic and staphylococcic infections. The author has drawn some implications applicable to penicillin therapy in syphilis from these studies which could well have been summarized in a footnote.

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## Dedication

### TRIBUTE TO DR. FOX

This issue is dedicated to Dr. Howard Fox to commemorate his scientific, academic and editorial contributions to dermatology. He resigned as Chief Editor of the ARCHIVES OF DERMATOLOGY AND SYPHILIOLOGY in March 1947, after serving with distinction in this capacity for ten years and bringing the ARCHIVES through what was probably its most difficult period.

The contributors to this issue, with the exception of Dr. MacKee, are former associates of Dr. Fox. All of them spent varying periods of time in his office, and their articles are listed according to seniority in service.

We are happy that Dr. Fox is able to appreciate these contributions of his colleagues, and it is hoped that he has extended years of good health and continuous activity.

EDITORIAL BOARD.

tasis. Thus, the difficulty in the eradication of metastases was the most common cause of failure. In only 3 cases was an attempt made to dissect out the nodes. In the remaining cases the extent of metastatic spread or the poor general condition of the patients contraindicated any treatment except palliative roentgen ray therapy, which was given in several instances.

#### THERAPEUTIC RESULTS IN OTHER NEOPLASTIC AND PRENEOPLASTIC LESIONS OF THE FACE

The microscopic control of excision provided by the chemosurgical technic is also useful in the treatment of other neoplastic and preneoplastic lesions of the face.

*Fibroma*.—Four fibromas, 2 of the neck and 2 of the scalp, were chemosurgically excised with satisfactory results. There has not been any recurrence after periods of from four months to two years.

TABLE 5.—*Effect of Site of Origin of Squamous Cell Epithelioma on Prognosis*

Site	Number of Lesions	Successful Results	
		Number	Percentage
Upper lip (skin).....	3	3	100.0
Cheek.....	33	30	90.9
Neck.....	10	9	90.0
Forehead .....	6	5	83.3
Temple.....	14	10	71.4
Chin.....	2	1	50.0
Scalp.....	2	1	50.0
All sites.....	70	59	84.3

*Hemangioma*.—Twelve hemangiomas of the face were chemosurgically excised with satisfactory results and without recurrence after periods of observation up to five years. The microscopic control usually is not necessary, because the blood in the vessels turns black on coagulation by the fixative, while the surrounding tissue turns white. Therefore, the extent of the hemangiomatous tissue is easily visualized with the naked eye.

*Nevus*.—Sixty-four nevi were chemosurgically excised from the face without recurrence or complications after periods of observation up to eight years. The procedure includes a vertical section through the center of the chemosurgically excised specimen. If the nevus cells are observed to extend more deeply, the fixative is reapplied and a horizontal section is made through the bottom of the next excised layer. These precautions are taken to insure elimination of all of the nevus which, if incompletely removed, might lead to melanoma.

*Keratoses*.—A total of 164 keratoses were removed with the chemicals used in the chemosurgical technic, and not in any instance has cancerous change supervened after periods of observation up to eight years.

The silver salts when ingested or absorbed are deposited as metallic silver in the cutis vera. In biopsy specimens stained with methyl green pyronin they are shown as brown granules. Occupational chrysiasis and hydrargyria have not been reported. I have not seen any cases or reports of pigmentation from external occupational exposure to arsenic.

#### OCCUPATIONAL DYEING OF THE SKIN

Exposure to dyes or chemicals which have dyeing properties will discolor the skin and hair. Workers in dye factories, especially those who handle the finished dyes, will have the hands and less often the face stained by the dyes. This staining is usually superficial and can be removed totally or partially by suitable washing. Soaking the hands in 1 to 2,000 potassium permanganate solution for a minute, immersion in 2 per cent solution of potassium bisulfite to remove the permanganate stain and then washing with soap and water is a method used in one factory to remove dye from the hands.

The hands, face and hair of munition workers handling tetraniromethylaniline (tetryl), trinitrotoluene (TNT), dinitrotoluene (DNT), penta erythryltetranitrate (PETN), trinitrophenol, ammonium picrate, lead styphnate and hexanitrodiphenylamine are often yellowish from contact with these chemicals.<sup>8</sup> The term "canaries" and "tetryl blondes" are applied to workers whose hair is dyed with tetryl. Norwood<sup>9</sup> devised an indicator soap which is a soft soap containing potassium sulfite to remove tetryl and trinitrotoluene from the skin.

The hair of workers coming in contact with large amounts of sodium carbonate is bleached yellow. "Atabrine" (quinacrine hydrochloride) taken by our armed forces caused a yellow discoloration due to the deposition of the dye in the skin. Systemic poisoning with such chemicals as the chlorinated hydrocarbons which injure the liver may cause jaundice from deposition of the bile pigments in the skin.

#### OCCUPATIONAL DEPIGMENTATION OF THE SKIN

Depigmentation of areas of the skin which were previously sites of deep-seated occupational dermatitis is occasionally seen. Occupationally incurred scars, the result of burns, loss of skin resulting from wounds and cutaneous infections are usually depigmented. Although depigmentation not infrequently occurs in sites of healed arsenical dermatitis resulting from arsphenamine treatment of syphilis,

8. Schwartz L.: Dermatitis from Explosives, J.A.M.A. **125**:186-190 (May 20) 1944.

9. Norwood, W. D.: Trinitrotoluene (TNT): Its Effective Removal from the Skin by a Special Soap, Indust. Med. **12**:206-208 (April) 1943.

## PROPIONATE-CAPRYLATE MIXTURES IN THE TREATMENT OF DERMATOMYCOSES

With a Review of Fatty Acid Therapy in General

SAMUEL M. PECK, M.D.

AND

WALTER R. RUSS, B.S.

NEW YORK

THE USE of the fatty acids in the treatment of mycotic infections was introduced by Peck and his associates.<sup>1</sup> They were led to this treatment because their investigations had convinced them that human perspiration played a role as a protective mantle against infections generally and fungous infections in particular. The basis for their treatment was founded on the fact that they were able to demonstrate that sweat was fungicidal and fungistatic, because of its content of fatty acids. Previous investigations on the fatty acid series from C<sub>1</sub> to C<sub>11</sub> by Peck and Rosenfeld<sup>2</sup> had demonstrated that the fatty acids inhibited growth of pathogenic fungi and that in proper concentration many of them were fungicidal. Since then many investigators have confirmed the therapeutic value of fatty acids in mycotic diseases.

It is important to emphasize that the use of fatty acids is an advance in treatment, not because new and startlingly effective fungicides have been introduced but because a more physiologic approach to the treatment of fungous infections has been proposed. Since these therapeutic agents are more physiologic in their origin, they tend to be less irritating and thus decrease the occurrence of local irritation and the development of dermatophytids, which are often complicating sequelae of the use of many fungicidal chemicals.

Marchionini and Cerutti<sup>3</sup> suggested that the hydrogen ion concentration of the sweat as such was important in protecting the skin against

1. Peck, S. M.; Rosenfeld, H.; Leifer, W., and Bierman, W.: Role of Sweat as a Fungicide, *Arch. Dermat. & Syph.* **39**:126-146 (Jan.) 1939.

2. Peck, S. M., and Rosenfeld, H.: The Effects of Hydrogen-Ion Concentration, Fatty Acids and Vitamin C on the Growth of Fungi, *J. Invest. Dermat.* **1**:237-265 (Aug.) 1938.

3. (a) Marchionini, A.: Untersuchungen ueber die Wasserstoffionenkonzentration der Haut, *Arch. f. Dermat. u. Syph.* **158**:290-333, 1929. (b) Marchionini, A., and Cerutti, P.: Untersuchungen ueber die Wasserstoffionenkonzentration des Schweißes bei Hautkrankheiten und deren Beziehung zur Alkali Reserve des Blutes, *ibid.* **170**:223-225, 1934.

proportion of recurrent lesions (27.1 per cent as compared with 14.3 per cent in Magnussen's series).

The unprecedented reliability of the chemosurgical method is not due to an excessively radical approach since only 1 or 2 mm. of tissue need be removed beyond the level of cancerous invasion. Both the reliability and the conservatism are the results of the systematic microscopic control of excision which is made possible by the chemosurgical technic.

The microscopic control is needed because of the strong tendency for epitheliomas to exhibit irregular and often unsuspected outgrowths from the main cancerous mass. These silent outgrowths are more common and more extensive in advanced and in recurrent epitheliomas, but they are not infrequently observed in early lesions as well.

Another advantage of the chemosurgical method is the practically complete lack of mortality due to the operation. This is an important feature, because many patients with epithelioma are elderly and in poor general health.

A disadvantage of the method is that specialized training and experience are required for the attainment of the best results.

#### SUMMARY AND CONCLUSIONS

The present series includes 232 basal cell epitheliomas and 103 squamous cell epitheliomas of the face treated by the chemosurgical method and observed for periods of three years or more.

Successful results were attained in 100 per cent of the cases of basal cell epithelioma of the face in the determinate groups in both the three year and five year periods of observation. These results were attained despite the fact that many of the cancers were advanced and over a third had recurred after previous unsuccessful treatment by means of surgical excision, irradiation or caustics.

Successful results were attained in 84.3 per cent of the cases of squamous cell epithelioma in the determinate group in the three year period even though many of the cancers were advanced; 27.1 per cent had recurred after previous treatment and 11.4 per cent had regional metastases. In the five year period of observation successful results were attained in 82.1 per cent of the cases.

The unprecedented reliability of the chemosurgical treatment of cancer of the face is attained by virtue of the systematic microscopic control of excision afforded by the technic. The microscopic control is important because of the frequent occurrence of small caliber, grossly undetectable outgrowths from the main cancerous mass. The reliability is not a result of an excessively radical approach, since only 1 or 2 mm. of tissue beyond the limits of cancerous invasion need be removed.

## SUMMARY AND CONCLUSION

A review of the experimental background and the clinical experiences with fatty acid therapy in the treatment of dermatomycoses is given. The results of in vitro experiments and clinical trial of a mixture of propionates and caprylates in various types of fungous infections are enumerated. The propionate-caprylate combination seems to be more effective than any of the other fatty acids tried for these diseases.

The research staff of the Ward Baking Co. provided the data included in the graphs.

140 East Fifty-Fourth Street.

scribed 1 Gm. three times a day beginning April 10, 1939. Sulfapyridine, 0.5 Gm., was administered three times a day thereafter for two weeks. During the first week of this treatment, the itching was greatly relieved and the vesicles and bullae began to disappear. At the end of the second week the pruritus, vesicles and bullae had completely disappeared, even though the dose had been reduced to a 0.5 Gm. tablet of sulfapyridine taken twice a day. The dose had been reduced gradually, so that the patient received half a tablet every other day for several weeks. The patient was presented again at a meeting on December 12.<sup>16b</sup> She had had no recurrence of the eruption, presenting only extensive areas of residual hyperpigmentation, hypopigmentation and superficial scarring. I have been in touch with the patient on a number of occasions since that time. She has married, has had one child and has never had the slightest recurrence of this rebellious disease. Dr. Howard Fox<sup>16</sup> had seen this patient in consultation before sulfapyridine was administered and on several occasions since her recovery. He stated that "she presented a typical picture of Duhring's disease and the result was striking." This patient, the first one reported by me as treated successfully with sulfapyridine for dermatitis herpetiformis, was cured of the disease.

As a result of this experience and in view of the fact that a number of reports have appeared since in dermatologic literature both here and abroad (Barber<sup>17</sup>) regarding the efficacy of the sulfonamide drugs, especially sulfapyridine, in the treatment of dermatitis herpetiformis, I thought that it would prove of interest and value if a simple questionnaire were sent to the members of the American Dermatological Association to determine the present status of sulfapyridine in the treatment of dermatitis herpetiformis.

In reply to question 1—Do you believe that the sulfonamide drugs are of value in the treatment of dermatitis herpetiformis?—of 100 members 59 said yes, 1 stated probably, 5 that they were of some value, 23 that they had little or no experience in treatment with these drugs, 11 that they were of doubtful value and 1 member (United States Navy) that he was not at liberty to disclose his observations. Therefore, 85 per cent of those members who had experience with the sulfonamide drugs thought that they were of value in the treatment of dermatitis herpetiformis. In reply to question 2—Do you think that sulfapyridine is the most effective sulfonamide drug in the treatment of dermatitis herpetiformis?—54 of 100 said yes, 5 said no, 2 stated probably, 1 said that he had used the other sulfonamide drugs in preference to sulfapyridine, 23 said that they had little or no experience, 8 were doubtful,

16. Fox, H., in discussion on Costello.<sup>15b</sup>

17. Barber, H. W.: The Sulphonamides in Dermatology, Practitioner 152: 281 (May) 1944.

areas of squamous epithelium. None of the 8 tumors showed connections with the epidermis. In 5 of the 8 tumors partial keratinization of the squamous cells was present. It is my belief that several of the 8 tumors were benign tumors of sweat glands rather than carcinomas of sweat glands. A short review of the 8 tumors is given here.

Cornil<sup>3</sup> described a tumor which had been present on the scrotum of a 59 year old patient for six months and which had become ulcerated. The tumor was a squamous cell epithelioma. At the periphery of the lesion Cornil noted the presence of hypertrophic sweat glands with metamorphosis of glandular cells into squamous cells. There were no connections between these sweat glands and the squamous cell epithelioma.

Hufschmitt and Diss<sup>4</sup> observed a patient in whom, at the age of 37, a solitary tumor had appeared on the scalp. After excision, at the age of 57, the tumor recurred and numerous others formed in its vicinity, so that, at the age of 61, three quarters of the scalp was covered with tumors. Some of them were ulcerated, and others were not. Histologic examination revealed that the tumors were composed of sharply outlined epithelial strands which at first sight were suggestive to the authors of basal cell epithelioma. However, most of the cells were connected by intercellular bridges. No development into horn cells was observed. Because of the presence of true glandular lumens in almost every epithelial strand, the authors concluded that the tumors represented carcinoma of the sweat glands.

Grynfeltt<sup>5</sup> reported a solitary small nonulcerated tumor which had been present for five years in the left inguinal region of a woman aged 26. Histologic examination revealed a tumor composed of lobules of various sizes. The lobules contained glandular lumens surrounded by cells of two types. They corresponded to the two types of cells which form the inner and the outer layer of normal sweat ducts. The tumor was composed mainly of cells of the outer layer. Many of them showed intercellular bridges, though less distinctly than the cells of the normal epidermis. There was no evidence of cornification.

The tumors reported by Ruge<sup>6</sup> and Schiffmann<sup>7</sup> were located on the labia majora. Histologically, they were glandular tumors with numerous papillary projections into their lumens. It is my belief that

3. Cornil, V.: Contributions à l'histoire du développement histologique des tumeurs épithéliales, *J. de l'anat. et physiol.* **2**:476, 1865.

4. Hufschmitt and Diss: Epithélioma sudoripare, *Bull. Soc. franç. de dermat. et syph.* **36**:503, 1929.

5. Grynfeltt, E.: Tumeur sudorifère de la région inguinale, *Bull. Assoc. franç. p. l'étude du cancer* **18**:64, 1929.

6. Ruge, H.: Ueber Vulvaaffektionen und ihre gynäkologische Bedeutung (Schweissdrüsencarcinome), *Ztschr. f. Geburtsh. u. Gynäk.* **56**:307, 1905.

7. Schiffmann, J.: Schweissdrüsencancroid der Vulva, *Zentralbl. f. Gynäk.* **44**:59, 1920.

3 for four months, 7 for three months, 2 for two months, 2 for six weeks, 3 for one month, 2 for three weeks, 1 for two weeks, 3 for one week, 10 stated that they did not have sufficient experience to give an opinion and 23 had no experience. In reply to question 10—Do you consider the continued or the interrupted form of treatment more successful?—of 99 members 25 were in favor of the continued form of treatment, 19 were in favor of the interrupted form, 27 were indefinite and 28 had little or no experience.

The toxic reactions of sulfapyridine are relatively frequent, requiring careful administration of the drug and close observation of the patient. They seldom occur singly. It might not be amiss to list the common toxic manifestations encountered, such as (1) nausea with vomiting, which is probably due to the effect of the drug on the central nervous system, (2) cyanosis, a minor toxic symptom; and (3) eruptions due to drugs, the intensity of which increases in severity with photosensitivity (it is therefore suggested that patients who are receiving this drug should not be exposed to strong sunlight). Morbilliform, bullous and exfoliating eruptions have been reported. Omens and Robbins<sup>18</sup> recorded a severe toxic bullous eruption following the use of sulfapyridine. A superimposed eruption of this type occurring during treatment may be mistaken for an exacerbation of dermatitis herpetiformis. The continued administration of the drug in such circumstances may result in severe consequences. I have seen a number of generalized morbilliform and purpuric eruptions following the administration of sulfapyridine. LaRocco<sup>19</sup> had a similar experience. Oliver<sup>20</sup> informed me of the death of a 49 year old woman who suffered from dermatitis herpetiformis and in whom erythema exudativum multiforme bullosum (erythema bullosum malignans of the pluriorificial type) developed in the fourth week of conservative medication with sulfapyridine. She had received a total of 45 Gm. of the drug.

Sherlock and White<sup>21</sup> reported a fatal case of acute purpura occurring during a course of sulfapyridine therapy for pneumonia. In view of the high rate of mortality in patients with purpuric eruptions, all patients receiving sulfonamide drugs should be watched for extraneous bleeding. (4) Thermic reactions occur. They are to be differentiated from fever caused by infection by the fact that there is no change in the leukocyte count or there is a diminution rather than an increase

18. Omens, D. V., and Robbins, J. B.: Severe Toxic Bullous Eruption Following the Use of Sulfapyridine, *Arch. Dermat. & Syph.* **40**:633 (Oct.) 1939.

19. LaRocco, C. G.: Sulfapyridine Dermatitis: Report of Two Cases, *Arch. Dermat. & Syph.* **42**:341 (Aug.) 1940.

20. Oliver, E. A.: Personal communication to the author.

21. Sherlock, S., and White, J. C.: Fatal Purpura After Sulphapyridine, *Brit. M. J.* **2**:401 (Sept. 23) 1944.

## COMMENT

Not all patients with dermatitis herpetiformis improve with sulfonamide therapy. Other patients thought to have dermatitis herpetiformis do not respond favorably because they have erythema multiforme bullousum, pemphigus vulgaris or infection with *Trichophyton purpureum*, simulating and mistaken for dermatitis herpetiformis.

On several occasions I have observed a type of mild dermatitis herpetiformis, consisting of pinhead-sized to match head-sized urticarial folliculopapules occurring especially in the axillas and inguinal and abdominal areas. Not more than a few thin-walled easily ruptured vesicles can be seen. A diagnosis of urticaria may be made on first observation, folliculitis on the second and dermatitis herpetiformis on the third. At times the diagnosis is made only after favorable response to the sulfonamide drugs.

I have been impressed with the number of patients suffering from dermatitis herpetiformis who also had infections of the respiratory tract, including pneumonia, pneumonic bacteremia, chronic bronchitis, asthma and bronchiectasis. Chronic discharging otitis media is also seen occasionally in these patients. It is possible that the custom of prescribing the solution of potassium iodide for chronic pulmonary infections may be a contributory factor in the causation of this dermatosis.

The oral administration of the iodides frequently causes exacerbation of dermatitis herpetiformis. A young army major had a severe recurrence of dermatitis herpetiformis, which had been controlled with sulfapyridine, when he accidentally aspirated through a pipette a solution of iodine in performing a laboratory experiment. The symptoms occurred four hours later and lasted about four days.

A pruritic eruption, indistinguishable from dermatitis herpetiformis, occurred repeatedly in a 64 year old man each time 8 drops of potassium iodide was administered for a cardiovascular disease.

My colleagues and I were able to observe elevation of temperature in patients in the wards at Bellevue Hospital. The degree of elevation was dependent on the extent, severity and character of the eruption. An elevation of temperature between 100 and 101 F. was not uncommon. On occasion it ranged between 101 and 103 F.

The eosinophil count varied. It was usually above 7 per cent, although it may be lower. Eosinophil counts from 12 to 35 per cent were occasionally observed. Whitfield<sup>42</sup> expressed the thought that a decided increase in eosinophilis was important in differentiating Duhring's disease from pemphigus vulgaris. An initial elevated leukocyte

42. Whitfield, A. W., in discussion on Weber, F. P.: Chronic Pemphigus or Dermatitis Herpetiformis in a Child, Proc. Roy. Soc. Med. (Sect. Dermat.) 21: 3, 1927.

noticed four months previously. Examination revealed a hard, raised, verrucous, centrally ulcerated tumor measuring approximately 1.5 cm. in diameter. The regional lymph nodes were not enlarged. The lesion was excised. When the patient was last seen, in June 1943, there had been no recurrence of the lesion.

*Histologic Examination.*—The tumor was surrounded by a broad band of granulation tissue. Islands of tumor tissue were present within the granulation tissue (fig. 1).

The epidermis was absent over part of the tumor. In areas where the epidermis was preserved it showed hyperkeratosis and considerable acanthosis. Numerous thick branching protrusions extended from the epidermis into the corium. These epidermal protrusions were composed of squamous cells which in many areas showed concentric arrangement with central cornification. In several areas, cornified

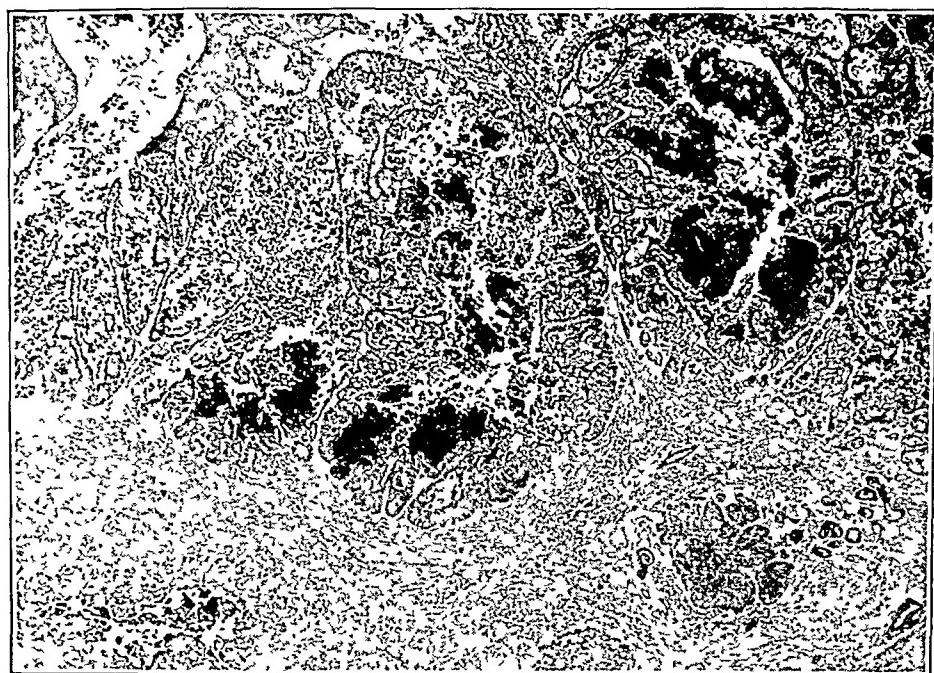


Fig. 1 (case 1).—The tumor contains large alveolar spaces into which papillary projections protrude and which are filled with desquamated cells. In the granulation tissue beneath the alveolar formations three islands of tumor tissue and several atypical sweat glands or ducts are present.

cells filled, either partially or completely, round to oval ductlike lumens (fig. 2) which suggested in their appearance intraepidermal sweat ducts. Many cells were atypical in appearance. A small number of mitotic figures were present. This part of the tumor was suggestive of squamous cell epithelioma.

From some of the epidermal protrusions long thin strands of epithelial cells extended into the corium. These strands usually consisted of only a single row of cells and enclosed large alveolar spaces. At their fundi, the alveolar spaces were lined by several layers of epithelial cells. Some of the alveolar formations lay so close to one another that only a thin layer of connective tissue separated their epithelial linings. Numerous papillary projections protruded from the walls

## ABSTRACT OF DISCUSSION

DR. GEORGE C. ANDREWS, New York: I congratulate Dr. Costello on his attempt to improve our knowledge of this important subject.

The benefits of sulfapyridine in the treatment of dermatitis herpetiformis are well established, but the serious reactions to the drug are a real drawback. That the benefits are due almost entirely to the sulfanilyl radical seems likely, because in many cases of dermatitis herpetiformis penicillin injections give good results.

Therefore, it seems that the bactericidal effects explain the beneficial action of these two drugs, which are chemically entirely unrelated, on this disease.

However, one must consider the pyridine radical. Pyridine in toxic doses produces paralysis of motor centers and nerve and thereby great muscular weakness and eventual death from failure of respiration. Amidopyrine is an effective hypnotic, antispasmodic and sedative. "Pyribenzamine hydrochloride" N. N. R. (tripelennamine hydrochloride), which is used beneficially in some cases of dermatitis herpetiformis, contains the pyridine radical and a benzyl ring.

Both sulfapyridine and "pyribenzamine" possess the sharp bitter taste characteristic of the pyridine radical. Perhaps in the near future some new drug will be discovered which will be effective in the treatment of dermatitis herpetiformis, with less danger of side effects.

The number of reactions from sulfonamide drugs and penicillin among new patients applying for admission to hospitals is a cause for some anxiety. Although many of the reactions are mild, others are serious.

I have in mind a patient who was shown at a meeting because of the remarkable benefit caused by sulfapyridine in the treatment of dermatitis herpetiformis. The next week she was admitted to the ward with high temperature, a generalized erythema multiform type of eruption from the drug, an erythrocyte sedimentation reaction of 135 mm., a leukocyte count of 28,000, a palpable liver and spleen and a heavy trace of albumin in the urine.

Now she has been in the hospital, seriously sick, over four weeks. She still has a daily temperature between 103 to 105 F., an erythrocyte sedimentation reaction of 128 mm. and a leukocyte count of 36,000, with eosinophilia. She still has the enlarged liver and spleen, generalized adenopathy and a heavy trace of albumin and many red blood cells and casts in the urine. Biopsies have been made from the skin and glands to exclude periarteritis nodosa.

Such reactions emphasize the importance of Dr. Costello's statistics and further studies of this subject.

DR. EDWARD A. OLIVER, Chicago: I enjoyed Dr. Costello's paper, and I agree with him for the most part. My purpose in discussing this paper is to illustrate the fact that sulfapyridine is not a nontoxic drug. In fact, sulfapyridine is reputed to be one of the most toxic of the sulfonamide drugs.

In March 1946, a widow, 49 years of age, consulted me for a mild form of dermatitis herpetiformis. I gave her solution of potassium arsenite, starting with 3 drops three times a day and increasing to 6 drops. That dose was maintained until October. I used to see her at monthly intervals, because she lived 40 miles from Chicago.

She improved considerably. On October 9, I decided to try treatment with sulfapyridine. I had used it successfully in previous cases. I prescribed  $\frac{1}{2}$  Gm. four times a day, instructing her to take it with plenty of water and alkalis. In two weeks she was considerably improved. I then prescribed  $\frac{1}{2}$  Gm. three times a day for one week and twice a day for the following week.

He experienced generalized purpura with bullae, and, although he did not die, I lost a patient.

DR. MARION B. SULZBERGER, New York: I want to discuss a point of principle rather than the details that have been presented.

There is no doubt that in some cases sulfapyridine must act differently from the other sulfonamide drugs. The first case in which this difference in therapeutic effect was proved was that of a nurse, Y.S., reported by Dr. R. L. Baer and me (ARCH. DERMAT. & SYPH. 40:1019 [Dec.] 1939). As the sulfonamide drugs were introduced we gave this patient each new drug in turn: "neoprontosil," sulfanilamide and then sulfapyridine.

There was no response to the sulfonamide drugs until we administered sulfapyridine. The acrodermatitis continua cleared up within a few days after treatment with sulfapyridine was started. In many repetitions, we showed that none of the other sulfonamide drugs acted like sulfapyridine. There are now numerous such cases in the literature. Most recently I studied a case of severe dermatitis herpetiformis, in which various sulfonamide drugs available at present were tried, and nothing helped until sulfapyridine was given. Again the patient's disease cleared up promptly.

I think that it is important, because it is not generally realized that there are different results from the different drugs in the treatment of certain diseases. That is to say, while the disease in some cases will respond well to any of the sulfonamide drugs there are some in which the response is only to sulfapyridine. And, of course, there are many cases of dermatitis herpetiformis and of acrodermatitis continua in which none of the sulfonamide drugs, not even sulfapyridine, is effective.

DR. C. GUY LANE, Boston: I still want to add my word of caution to what has been voiced by other speakers.

Dr. Perrin H. Long, speaking recently in Boston on the use of sulfonamide drugs, commented on sulfapyridine in the treatment of dermatitis herpetiformis. Results were checked in the last 25 cases at the hospital with which I am associated. There were reactions from the drug in practically a third of the patients. I was interested in the fact that most of the patients with dermatitis herpetiformis recovered after the reaction had subsided.

That is not always true. There was a patient with a severe reaction only recently, a 74 year old woman who had been responding well to treatment with sulfapyridine. Before the vesicles and itching were entirely cleared treatment with the drug was discontinued, because she felt so miserable generally.

Some months later she again felt so miserable because of the blisters and itching that I told her daughter, who was a nurse, to test her with 1 tablet, 0.5 Gm. She had a severe reaction, which started within three hours after the tablet was given.

She had a decided reaction—a rise in temperature to 102.5 F. and severe pain in the region of the right kidney, for which morphine compound was given. She had no vesicles for another three days, but now she has many vesicles and bullae. However, I do not intend to give her sulfapyridine again.

I have seen reactions from sulfanilamide and from sulfapyridine. I observed that 7 of 26 persons could not tolerate the sulfonamide drug in the first year. Three showed poor tolerance immediately, and about 4 discovered the difficulty within six months. Other reactions appeared later. Thus, there has been a good deal of variety with regard to the reactions.

I believe that one should be cautious in the use of sulfapyridine, and yet, when it is the only drug with which relief can be obtained in some of these cases, I

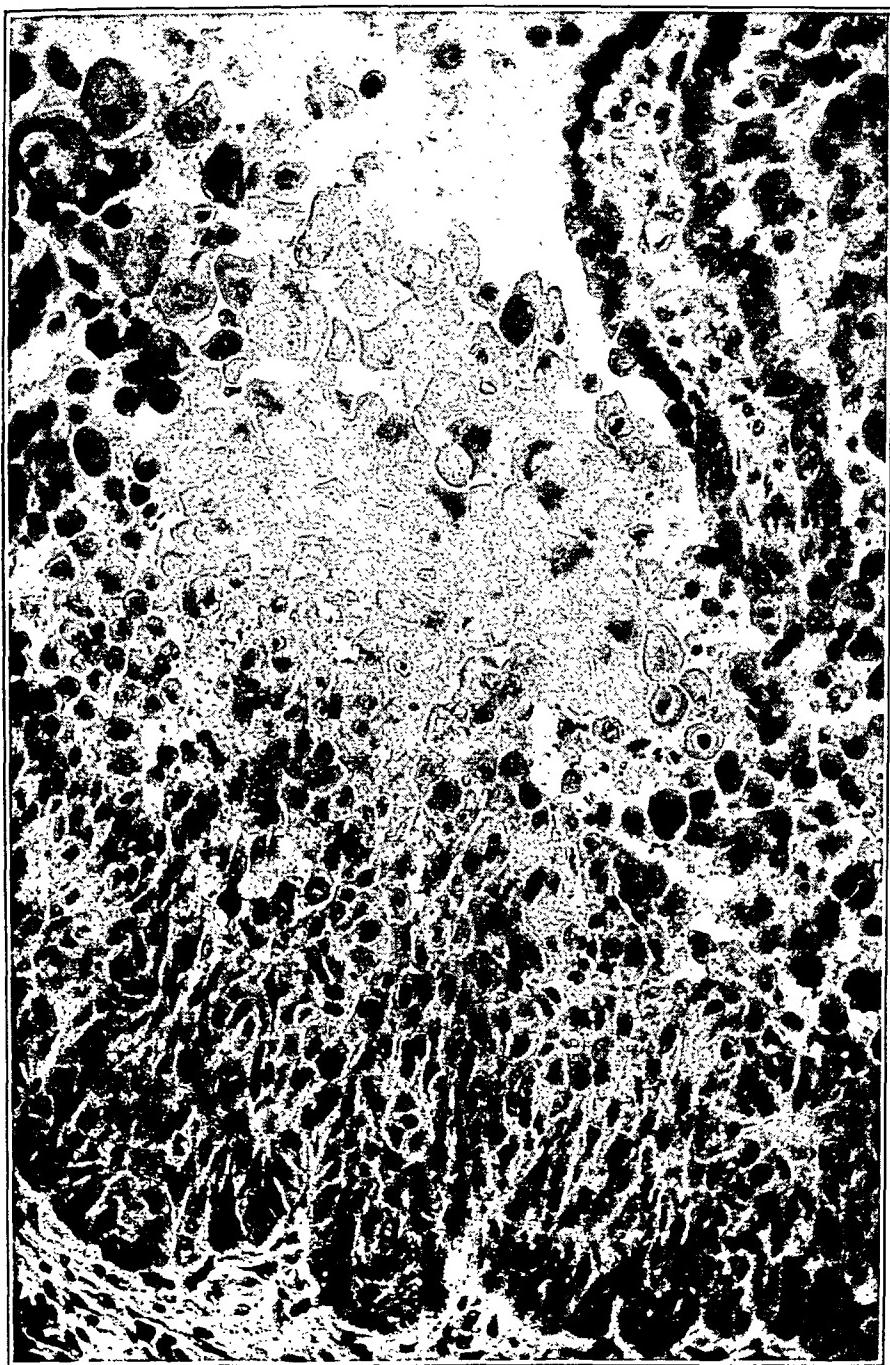


Fig. 3 (case 1).—High magnification of the fundus of an alveolar formation shows the presence of squamous cells and their development into cornified cells.

## PSORIASIS OF THE HANDS Nonpustular Type

MARCUS RAYNER CARO, M.D.

AND

FRANCIS EUGENE SENEAR, M.D.  
CHICAGO

DERMATOSSES of the hands at times pose a difficult problem in differential diagnosis. Lesions of chronic dermatophytosis, nummular eczema, chronic dermatitis and neurodermatitis on the hands may have so many features in common that often an accurate diagnosis cannot be made on clinical grounds alone. It would seem that adding another dermatosis to those already under consideration in the differential diagnosis in these cases would tend to complicate the problem still more. On the contrary, it has been our experience that not infrequently a case that does not seem to belong to any of the aforementioned diseases can definitely be identified as being psoriasis.

It is generally stated that psoriasis, exclusive of the pustular type, rarely affects the palms. For that reason psoriasis is seldom considered in the differential diagnosis of lesions on the hands that are not pustular or vesicular. We have felt for many years, however, on the basis of experience with a considerable number of cases, that there is an atypical form of psoriasis that affects the hands alone. It has been our experience that lesions of psoriasis on the hands are much more often papulo-squamous in nature than pustular.

Patients with generalized psoriasis will at times present papulo-squamous lesions also on the hands. In these cases the diagnosis of the lesions of the hands is made obvious by the characteristic generalized eruption. It has been our good fortune in several instances to observe patients in whom lesions only of the hands were present for a variable length of time and in whom other lesions of psoriasis later developed in more typical locations, thereby making the diagnosis more certain. In these patients and in several others in whom lesions of the hands only were present throughout the period of our observation, the diagnosis was definitely established by the characteristic histologic features in biopsy

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From the Department of Dermatology, University of Illinois College of Medicine.

are seen on the palms and finger tips. Not infrequently the lesions are confined to the fingers, the palms being spared. The lesions are bilateral and generally, but not always, symmetric. On the joints they tend to be rounded, while on the sides of the fingers and on the palmar surface they are more often ovoid, elongated or irregular in shape. Small papules may be seen on the joints, or a patch may be large enough to cover the entire side of a finger. Irrespective of size or shape, the lesions are always sharply circumscribed. They may be discrete or they may coalesce to form a patch with a polycyclic border. The lesions vary in color from

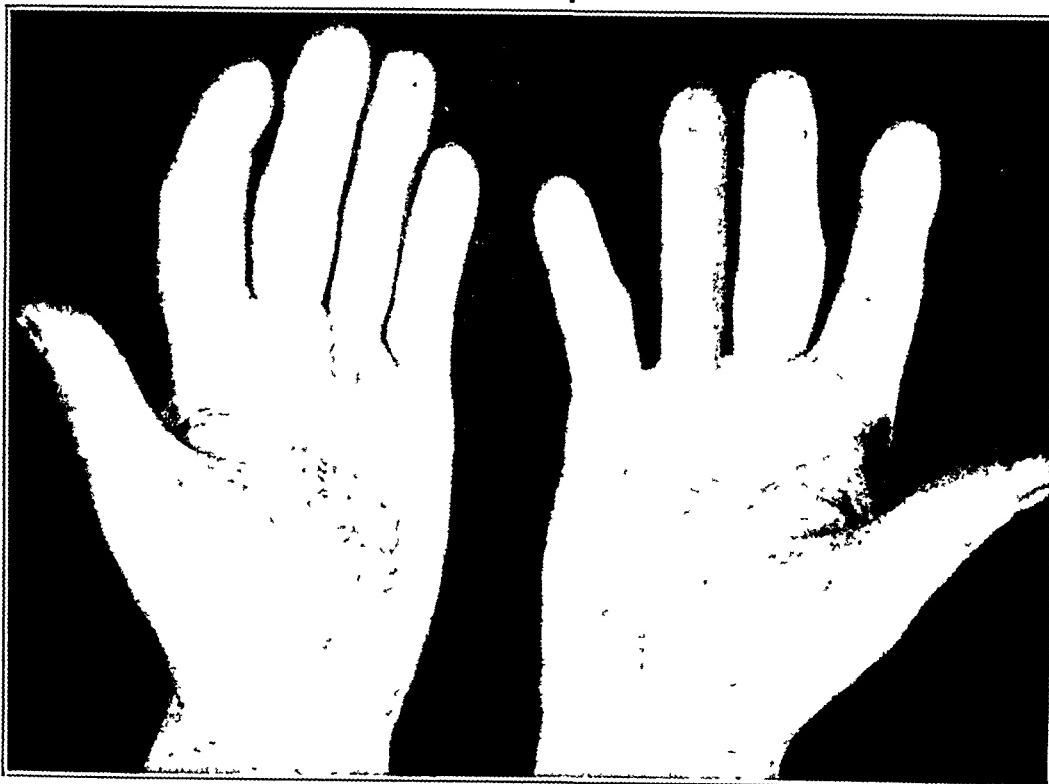


Fig. 2.—Typical lesions on the palms and finger tips. The patch on the right palm shows the characteristic saucer-shaped depression. The patches on the finger tips are fissured.

slight erythema to dusky brownish. On the joints the surface is often superficially knurled, and it is covered by a dry and sometimes glistening scale. On the joints and sides of the fingers the scale is thin, and it exhibits a silvery sheen only after scraping. On the palms and finger tips the scale tends to be thicker and more lamellated. There may be a slight peripheral overhanging scale, and there is a great tendency toward the development of fissures (fig. 2). On the finger tips especially the fissures may be deep and painful. In many lesions there is a saucer-like depression of the center to produce a characteristic dell which is more pronounced in larger patches.

lesion which he had first noticed six months previously. He presented on the anterior aspect of the right ear an indurated, slightly raised tumor which measured 4 by 6 mm. in diameter and had a granular surface covered with a crust. The lesion was excised.

*Histologic Examination.*—The epidermis showed a moderate degree of hyperkeratosis. In one area the epidermis showed atypical downgrowth consistent with squamous cell carcinoma. Irregular alveolar epithelial masses were connected with this area. Similar alveolar masses without apparent connections with the epidermis were seen elsewhere in the corium (fig. 5). The alveolar masses were predominantly solid, but nearly all contained cystic spaces of irregular outline. Most cells lining the cystic spaces were glandular cells. In areas, however, where the walls of the cysts consisted of several layers the cells nearest

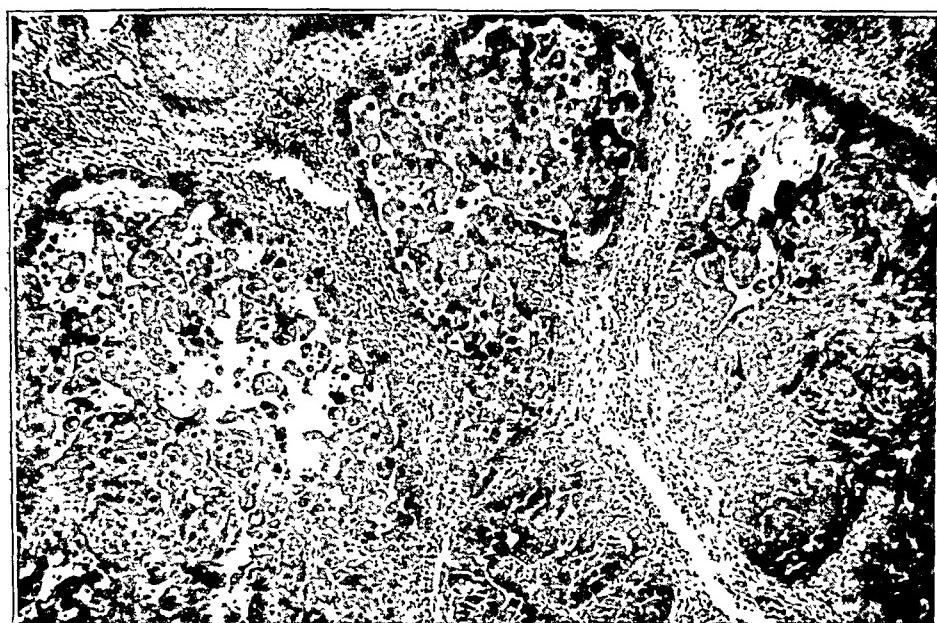


Fig. 5 (case 2).—Alveolar cell masses are located in the corium. The two, located at the left and in the center, are composed mainly of glandular cells and show large lumens containing desquamated, partially cornified cells. The alveolar mass at the right is predominantly solid. Some of its cells are squamous and cornified cells. Several whorls of epithelial cells are present. The cells in the center of the whorls are regarded as glandular, the cells at the periphery as myoepithelial cells. These formations probably represent anaplastic sweat glands.

to the lumen were squamous and partially cornified. The lumens contained desquamated cells showing various degrees of cornification. The solid parts of the alveolar masses contained, besides glandular cells, squamous and partially cornified cells. In addition, whorls of epithelial cells were present, which differed from horn pearls. The cells in the center of the whorls had round or oval nuclei, and those at the periphery had thin elongated nuclei. The central cells resembled glandular cells and the peripheral cells myoepithelial cells. It is possible that these formations represented anaplastic sweat glands. A few sweat ducts with considerable proliferation of their epithelium were seen at the base of the tumor.

The lesions in this type of psoriasis are extremely resistant to treatment.

SUMMARY

Attention is directed to cases of psoriasis of the hands in which the lesions are papulosquamous in nature. It is our opinion that these lesions are more frequently encountered in cases involving the hands than are lesions of pustular psoriasis. A biopsy is often necessary in these cases to differentiate psoriasis from all other papulosquamous dermatoses that occur on the hands.

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well bear this out. In addition, the fact that Wernicke's syndrome, the end picture of acute B<sub>1</sub> avitaminosis, so closely parallels arsenical encephalopathy directs attention to cocarboxylase.

Comparison of these two syndromes and the fact that peripheral neuritis is described as a not infrequent reaction to the five day drip led to the supposition that arsenical encephalopathy and acute vitamin B<sub>1</sub> deficiency have a common causation. A review of the role of thiamine in carbohydrate metabolism suggested that a study of patients undergoing intensive arsenical (five day drip) therapy for early syphilis might shed some further light on this important deduction. Such a study might determine whether the patient was primarily deficient in vitamin B<sub>1</sub> or was rendered deficient by arsenical administration and might determine the prophylactic or curative value of thiamine in reducing the cerebral complications due to arsenicals. Sherman and Elvehjem<sup>7</sup> finally proved that vitamin B<sub>1</sub>, in the form of diphosphate ester, is needed for the oxidative removal of pyruvic acid and indirectly of lactic acid. Extensive investigation has shown that both lactic acid and pyruvic acids accumulate in the blood and tissues and the pyruvic acid and other alpha-keto acids are excreted in increased amounts in the urine during the period of thiamine deficiency.

Levels of thiamine in the blood do not give a reliable estimation of the amount of diphosphothiamine functioning as the coenzyme in the tissues. Therefore, following the methods of Stotz and Bessey,<sup>8</sup> we used the ratio of lactatetolpyruvate in the blood to estimate the level of vitamin B<sub>1</sub>. This ratio takes into account all variables, such as anoxia from injections of dextrose and exercise. For every given level of lactic acid there is an associated level of pyruvic acid. If the level of pyruvic acid is higher than that given by the ratio, then that excess measures the state of deficiency. Determinations of lactic acid were made by the method of Elgart and Harris<sup>9</sup> with the modification of Koenman.<sup>10</sup> Determinations of pyruvic acid were made by the method of Friedemann, Haugen and Kmiecik.<sup>11</sup> The technic described by

7. Sherman, W. C., and Elvehjem, C. A.: In Vitro Action of Crystalline Vitamin B<sub>1</sub> on Pyruvic Acid Metabolism in Tissues from Polyneuritic Chicks, *Am. J. Physiol.* **117**:142, 1936.

8. Stotz, E., and Bessey, O. A.: The Blood Lactate-Pyruvate Relation and Its Use in Experimental Thiamine Deficiency in Pigeons, *J. Biol. Chem.* **143**: 625, 1942.

9. Elgart, S., and Harris, S.: The Determination of Lactic Acid in Blood. *Indust. & Engin. Chem.* **12**:758, 1940.

10. Koenman, R. H.: Modification of the Miller-Muntz Method for Colorimetric Determination of Lactic Acid, *J. Biol. Chem.* **135**:105, 1940.

11. Friedemann, T. E.; Haugen, G. E., and Kmiecik, T. C.: Pyruvic Acid: Level of Pyruvic and Lactic Acids and Lactic-Pyruvic Ratio in the Blood of Human Subjects; Effect of Food, Light Muscular Activity, and Anoxia at High Altitude, *J. Biol. Chem.* **157**:673, 1945.

August 1945 the patient presented on the upper free border of the right ear, in addition to several keratoses, a slightly indurated lesion measuring 6 mm. in diameter and covered by a heavy crust. Removal of the crust revealed a granular surface. The lesion, which was movable against the cartilage of the ear, was excised without injury to the cartilage.

*Histologic Examination.*—The epidermis was absent in the center of the lesion. At both margins of the ulcer the epidermis was hyperplastic, and alveolar formations originated from the epidermis. Other alveolar formations without visible connections with the epidermis were present in the corium. One of the alveolar formations was large, extending through the thickness of the corium, and the others were small: The alveolar formations possessed an epithelial lining which consisted in some areas of a single layer of cylindric cells and in others of several layers (fig. 6). Wherever there were several layers, the upper layers consisted

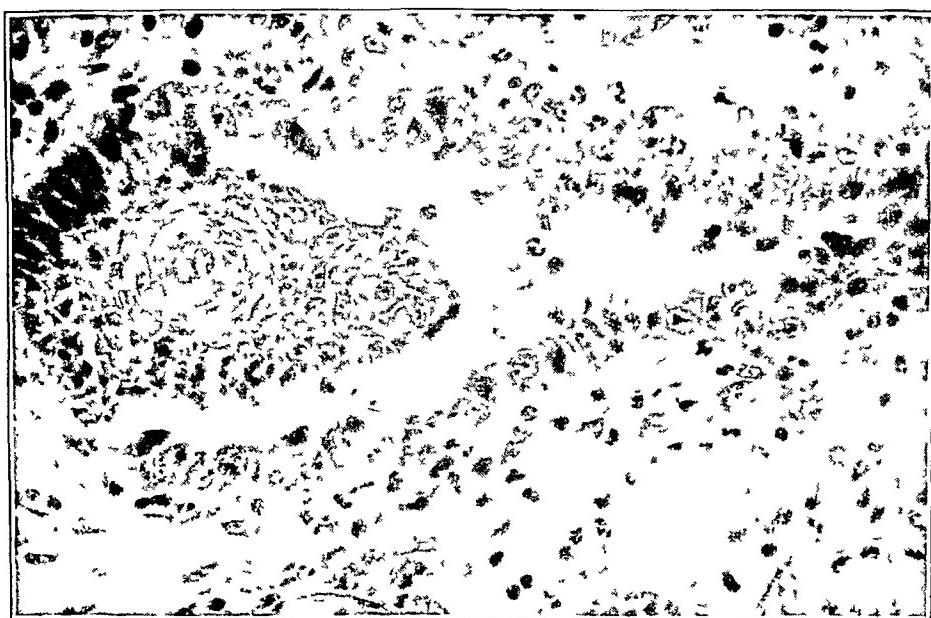


Fig. 7 (case 3).—A large glandular lumen, into which a papillary projection protrudes, is shown. The papillary projection is composed of squamous cells and contains a sweat duct.

of squamous and cornified cells which tended to desquamate into the lumen. There were papillary projections into the lumen lined with either one or several layers of epithelium. One of the smaller alveoli presented an interesting appearance (fig. 7). It was lined by a single layer of cylindric epithelial cells except in one area where there was a papillary protrusion which was composed of squamous cells and had in its center a sweat duct easily recognizable as such by the presence of an eosinophilic cuticle lining the lumen. There were in the corium several groups of sweat glands and ducts, none of which were abnormal.

**CASE 4.**—A 69 year old man was admitted to the hospital in November 1942 because of a lesion on his right ear which he had first noticed nine months previously and which had shown slow but steady growth since. Examination revealed

no irregularity, the muscular sensitivity was above normal. Pretreatment metabolic tests showed an elevated level of pyruvic acid and the blood sugar in the upper range of normal.

During the first day of treatment the lactic acid was more than double the "normal" level. The pyruvic acid remained high, coinciding with increased muscular sensitivity. The patient complained of pain in the back, arms and abdomen and was restless. As the treatment progressed he became weaker.

On the fourth night of treatment both the blood sugar and pyruvic acid were twice normal, with the lactic acid remaining normal. Petechial hemorrhages over the thighs and abdomen had broken out during the day. The patient was restless, perspired profusely and suffered from generalized pains and phlebitis at the sites of injection.

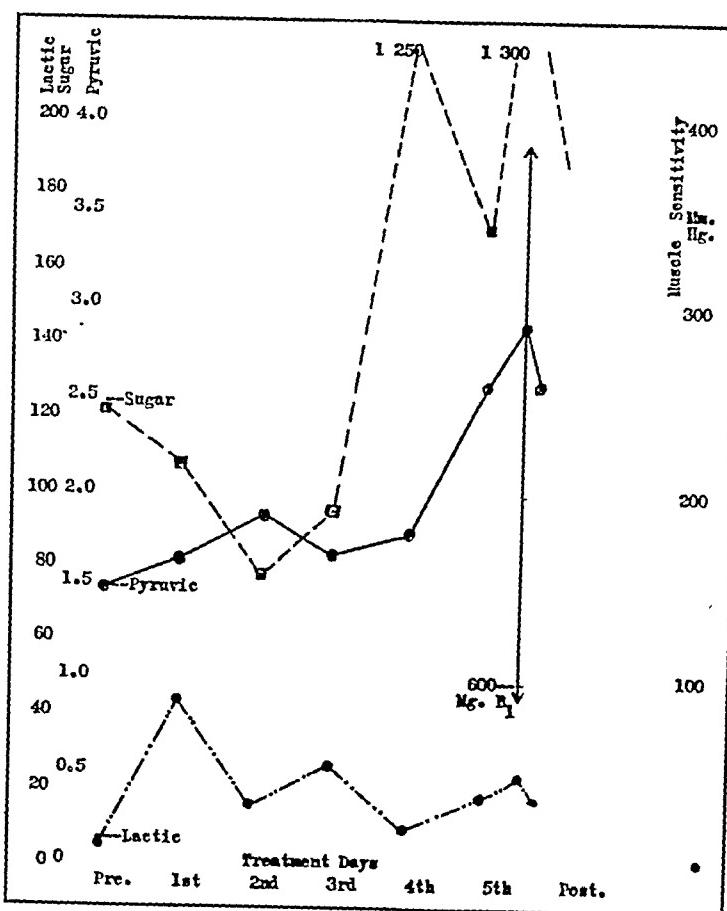


Fig. 2 (successful treatment).—Diagram illustrating a sharp rise in the level of pyruvic acid associated with arsenic toxicity and sharp reduction from vitamin B<sub>1</sub> therapy.

On the afternoon of the fifth and last day of treatment the level of pyruvic acid was 260 per cent of normal. The blood sugar and lactic acid increased somewhat, and the muscular sensitivity was greatly increased. On the evening of the same day the pyruvic acid had climbed to 290 per cent of normal, coinciding with the rise of blood sugar to over 300 mg. per hundred cubic centimeters. The muscular sensitivity was extreme, registering over 90 mm. of mercury (normal is 400). The patient had a severe headache, became disoriented and drowsy, appeared jaundiced and complained of tenderness in the region of the liver, and the temperature was 101.3 F. Six hundred milligrams of vitamin B<sub>1</sub> was given intravenously. Within half an hour the patient's muscular sensitivity had improved remarkably,

were originally diagnosed as xanthoma. A similar diagnosis was made by Sobel<sup>8</sup> in a case of a tumor of the upper lip.

The last review of cases of myoblastoma was made by Crane and Tremblay<sup>9</sup> in 1945; they added 5 of their own cases to 157 collected from the literature. In 1946, Powell<sup>4</sup> reported 4 cases, and in 1947, Simon<sup>10</sup> described 5 cases, which altogether make a total of 171 cases reported until now.

Since Abrikosoff<sup>11</sup> in 1926 introduced the term "myoblastic myoma" various similar names were used for this type of tumor: "myoblastoma," "granular cell myoblastoma," "granular cell rhabdomyoma" and others. These terms imply that these tumors are of myogenous origin, which theory is based on the resemblance of the granular cells to embryonic myoblasts. The most frequent location of myoblastoma is, as previously mentioned, on the tongue, followed in order of diminished frequency, by the skin and subcutis, muscle, maxilla, breast, larynx, vocal cord, mandible, lip, trachea, bronchus and ear.

#### CLINICAL FEATURES

Myoblastoma occurs mostly as a firm, nontender tumor, 0.5 to 2 cm. in diameter, round, well circumscribed and sometimes pedunculated or sessile. The overlying skin or mucous membrane is usually smooth, but may be hyperkeratotic and thickened, which point will be discussed in the comment on our case.

Although the vast majority of cases of myoblastoma were in adults, cases involving the alveolar process were chiefly in children, those involving the maxilla being in newborn infants. Such cases were reported, among others, by Crane and Tremblay<sup>9</sup> and by Battaglia and Curphey.<sup>6</sup> Cases reported as "congenital epulis of the newborn" belong in this group of tumors (Klemperer<sup>12</sup>).

#### HISTOLOGIC FEATURES

The most characteristic feature of myoblastoma is its composition of large granular cells which do not take fat stains. Two types of cells are described: (1) large, pale and polyhedral or ovoid and (2) larger elongated cells, arranged in ribbon-like and syncytial masses, some of which cells may show cross and longitudinal striations. Such

8. Sobel, N.: Personal communication to the author.

9. Crane, A. R., and Tremblay, R. G.: Myoblastoma, Am. J. Path. **21**:357 (March) 1945.

10. Simon, M. A.: Granular Cell Myoblastoma, Am. J. Clin. Path. **17**:302 (April) 1947.

11. Abrikosoff, A. I.: Ueber Myome ausgehend von der quergestreiften willkürlichen Muskulatur, Virchows Arch. f. path. Anat. **260**:215 1926.

12. Klemperer, P.: Myoblastoma of the Striated Muscle, Am. J. Cancer **20**: 324 (Feb.) 1934.

on the upper outer margin of the right ear a raised, round, papillomatous, centrally ulcerated tumor which measured about 1 cm. in diameter and was movable with the skin. There were no palpable lymph nodes. The tumor was excised.

*Histologic Examination.*—The epidermis was in part absent because of ulceration. In the areas where the epidermis was preserved it was hyperkeratotic and was the site of atypical proliferation consistent with squamous cell epithelioma. From the epidermal processes of the tumor long strands of epithelial cells branched out. The strands formed irregular convolutions which either were solid or possessed lumens (fig. 8). Most lumens were tubular, but a few were alveolar. The alveolar lumens had an irregular outline due to the presence of papillary projections into the lumens. Although most epithelial cells had the appearance of glandular cells, many lumens contained desquamated cells in various stages of keratinization and some of the solid convolutions showed in the center squamous and keratinized cells which occasionally were arranged in the form of horn pearls (fig. 8). The nuclei of the epithelial cells varied considerably in size and shape, and mitotic figures were numerous.

In various parts of the tumor, cross sections of small ducts were present. They were of two types (fig. 9). The ducts of the first type showed glandular epithelium and resembled dermal sweat ducts. Only few ducts of this type had a normal appearance. Most of them showed an irregularly shaped lumen due to the presence of papillary projections into the lumen. The other type of duct showed a slitlike lumen surrounded by an eosinophilic cuticle and by several layers of squamous cells. The presence of an eosinophilic cuticle identified these ducts as sweat ducts. Due to the presence of squamous cells they resembled cross sections of rete pegs containing a sweat duct. They were regarded as intraepidermal sweat ducts. Transitions from both types of sweat ducts to structures belonging to the tumor were observed.

#### COMMENT

All 4 tumors were observed in men whose ages ranged from 65 to 79. The tumors were all located on the head (3 of them on the ear). In each instance the tumor had been present for only a short time, varying from four to nine months. All 4 tumors were small in size. The smallest measured 6 mm. and the largest 1.5 cm. in diameter. In their clinical appearance the tumors were suggestive of squamous cell epithelioma rather than basal cell epithelioma. Two of the 4 tumors (cases 1 and 4) had a verrucous surface with central ulceration, and 2 (cases 2 and 3) had a granular surface covered with a crust. None of the tumors had caused metastases and none recurred following excision.

From the histologic point of view, the tumors were thought to be carcinomas because of their invasive growth, the atypicality of their epithelial cells with great variation in their size and shape and the presence of mitotic figures. The presence of lumens surrounded by columnar cells in all 4 tumors was suggestive of an origin from tubular glands. Within or close to the tumors eccrine sweat glands and ducts were seen. Some of them had a normal appearance, while others showed proliferation of their epithelium. In all cases, the appearance of the altered sweat glands and ducts approached that of parts of the tumor.

The pathologist stated that while these epidermal changes might be simply a reaction to the myoblastoma, there were sufficient changes present to call it a low grade squamous cell carcinoma. In view of these remarks the patient was urged by letter to return to the clinic for further observation and treatment. However because of a change of address, the patient did not receive our communication. Two years later, on March 24, 1947, a dermatologic consultation

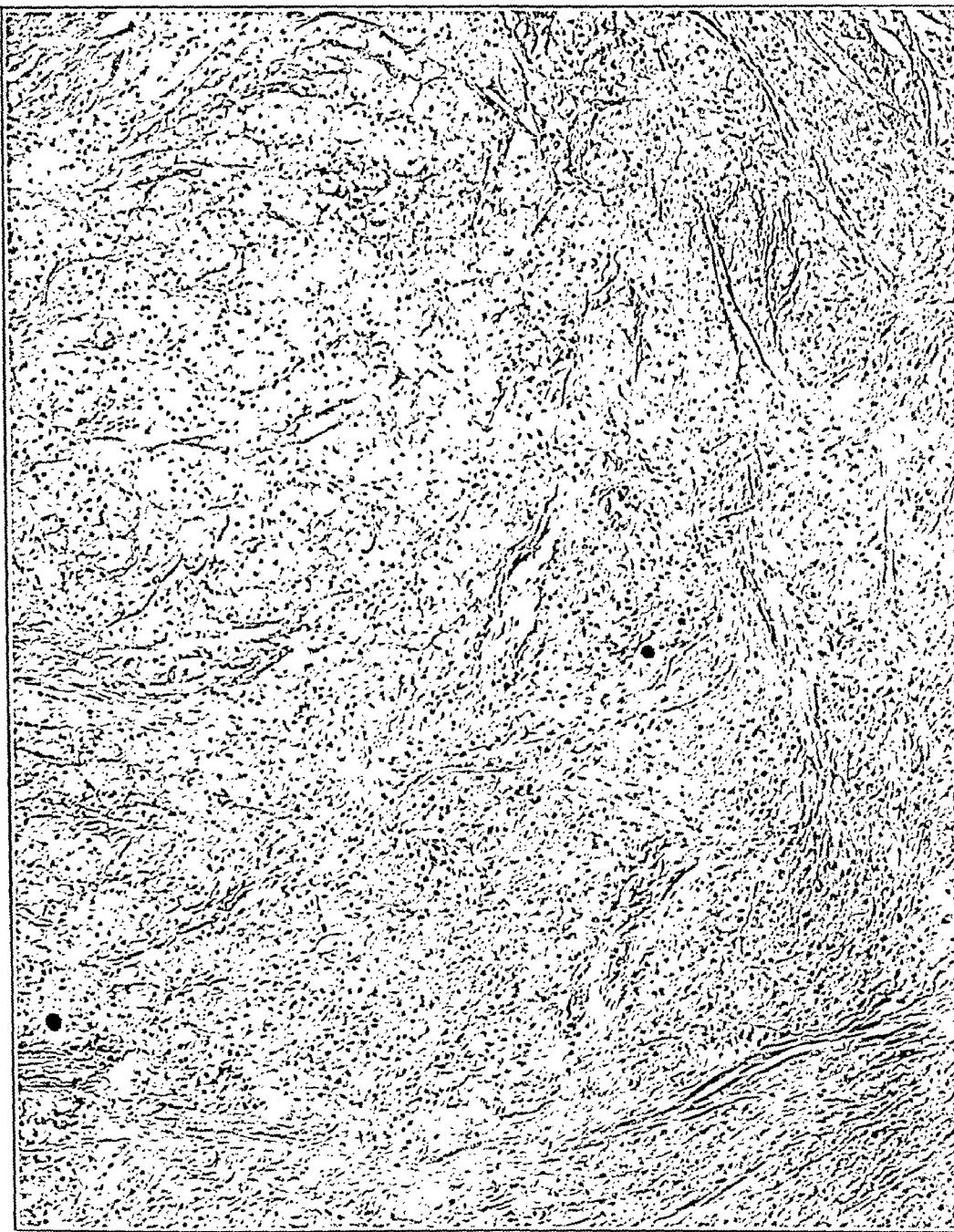


Fig. 2.—Section from the tumor of the skin, showing characteristic granular "myoblastoma" cells and collagen fibers of the corium ( $\times$  approximately 81).

was requested on this patient, who had been admitted because of pneumonia to the Sydenham Hospital, on the service of Dr. Jacob Heiman.

On examination, there were seen several cutaneous tumors: a hazelnut-sized firm nodule was attached to the skin and subcutis on the inner aspect of the right

on October 10, in the care of his family physician who continued the administration of vaccine intradermally every five days. The diagnosis on discharge was recorded as papilloma, squamous cell type, of the skin of the penis.

The patient was extremely uncooperative and did not return for follow-up observation, nor did he continue treatment with his local physician.

*Second Period of Hospitalization.*—On July 12, 1946, the patient was again hospitalized. The fungating granulomatous masses had spread to encompass all the skin of the penis (fig. 3). Results of the physical examination were again essentially negative, except for these lesions. There was no involvement of the inguinal glands or the scrotum. The skin of the penis was displaced by a red foul-smelling ulcerative hyperplastic mass. The penis was distorted and monstrous

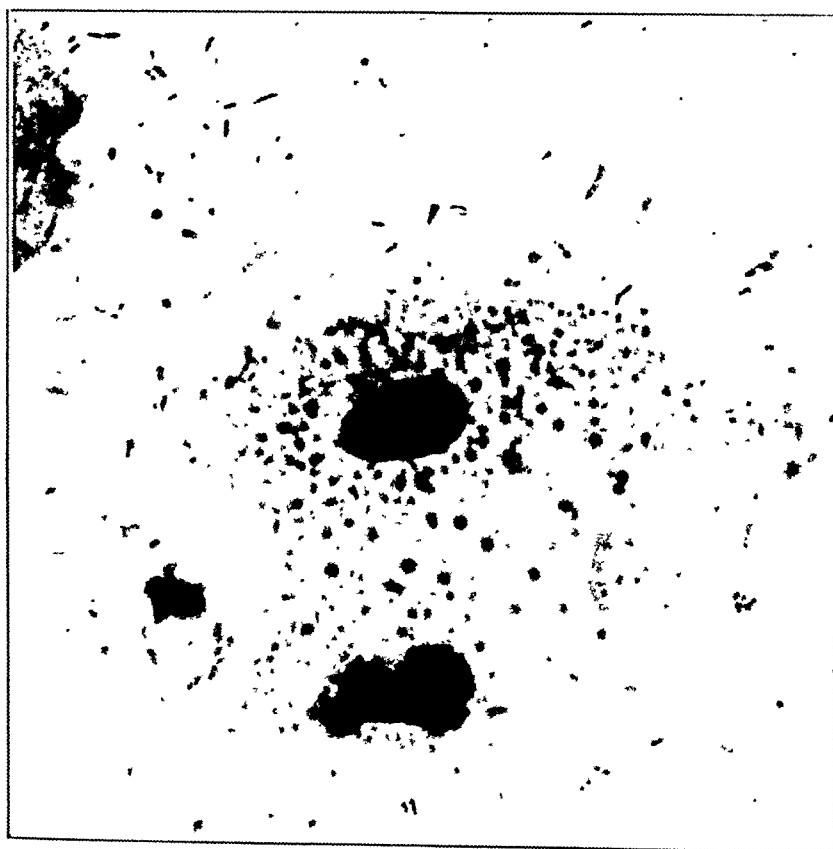


Fig. 4.—Photomicrograph ( $\times 1,200$ ) of tissue removed from the depths of the granulomatous mass, showing large monocytes and numerous Donovan bodies.

and measured approximately 11 inches (27.94 cm.) in circumference. On some areas smooth reddened firm masses were present, while in others the ulcerative cauliflower-like nature was apparent. There was a particularly foul-smelling discharge.

Presumptive diagnoses at this time were (1) carcinoma of the penis and (2) granuloma inguinale.

*Treatment.*—The patient was given penicillin, 40,000 units every three hours, combined with local wet packs of "chloresium solution-plain" (water-soluble derivatives of chlorophyll "a" in isotonic solution of sodium chloride). All previous diagnostic tests and laboratory and biologic procedures were repeated, with essentially the same results.

First, these tumors may be adenocarcinomas with metaplasia of glandular into squamous epithelium. The presence of various stages of development of glandular cells into squamous and keratinized cells is in favor of this theory. Or, second, these tumors may represent carcinomas of the epidermal as well as of the dermal parts of sweat ducts. Since inside the epidermis the walls of the sweat ducts are formed by squamous cells and not by glandular cells (fig. 10), it is believed possible that carcinomatous anaplasia affecting the sweat ducts may produce not only an adenocarcinoma but also a squamous cell epithelioma. In other words, the tumors may carry out both potentialities inherent to the tissue from which they originate. The presence of squamous cell epithelioma inside the epidermis in the tumors of cases 1, 2 and 4, the presence in the epidermis of ductlike lumens filled with cornified cells in case 1 and the presence of sweat ducts with walls composed of squamous cells deep in the tumors of cases 3 and 4 are factors in favor of the second theory. Though the second theory appears more plausible, it is possible that the mechanics of both theories combined in the genesis of these tumors.

It is surprising that only one author, namely Deichstetter,<sup>10</sup> has described a tumor of this type, whereas 4 such tumors were observed at one hospital within four years. It is likely that tumors of this type have previously been regarded either as squamous cell epithelioma with degeneration in the center of the tumor masses or as basal cell epithelioma. For instance, Ewing's book on neoplastic diseases<sup>12</sup> contains the photograph of a tumor similar in appearance to the tumors in cases 2 and 3 which was regarded by Ewing as a basal cell epithelioma.

The designation adenoacanthoma of sweat glands is suggested for these tumors. The term adenoacanthoma has been chosen because it is already in use for tumors composed of glandular and squamous elements. Such tumors have been described as occurring mainly in the corpus uteri, but occasionally also in the esophagus and other organs.

#### SUMMARY

Carcinoma of the sweat glands containing glandular as well as epidermal structures have only rarely been mentioned in the literature and have so far not found recognition as a distinct type of carcinoma of the sweat glands. Four such tumors were observed at the Massachusetts General Hospital.

These tumors show tubular and alveolar lumens lined with one or several layers of epithelium. In areas where the lumens are lined with a single layer of epithelial cells have the appearance

12. Ewing, J.: Neoplastic Diseases, ed. 4. Philadelphia. W. B. Saunders Company, 1940, p. 903.

the corresponding subepidermic zone there were many similar small round cells. The superficial blood vessels were dilated, with a nonspecific perivascular inflammatory reaction of small round cells and wandering connective tissue cells. The lumens of the vessels contained many leukocytes. There was some interstitial edema of the cutis. The histologic diagnosis was contact eczematous dermatitis with beginning vesicular formation.

CASE 6.—F. P., a hairdresser, aged 48 years, presented erythematovesicular patches on the fingers and hands, which he stated had existed for one year. He

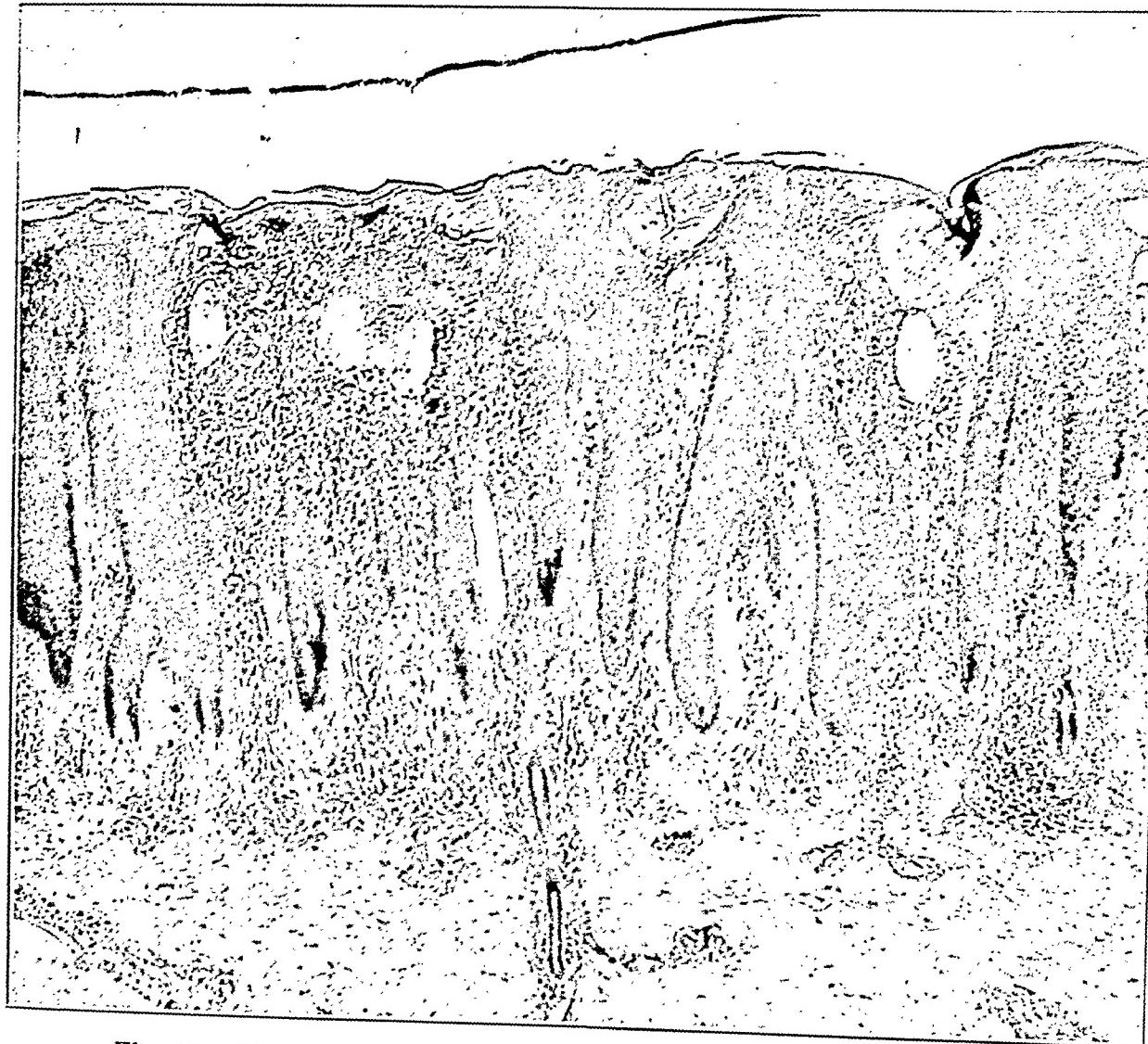


Fig. 11.—Eczema. The epidermis is irregularly acanthotic. There is intercellular edema, spongiosis and primary vesicular formation. The cutis shows dilatation of the capillaries in the papillary bodies and the superficial blood vessels. These vascular elements are surrounded by wandering connective tissue cells and small round cells. ( $\times 30$ .)

said that similar patches occasionally appeared on his face and legs. Many substances were applied in patch tests. A positive response was obtained to "clairoil" hair dye. The clinical diagnosis was contact eczematous dermatitis of occupational origin.

Microscopic examination (fig. 9) revealed that the superficial blood vessels were dilated. There was a decided perivascular inflammatory reaction composed

*Dyshidrosis.*—In true dyshidrosis a characteristic feature is the vesicle within the epidermis. This vesicle is in the intraepidermic portion of the sweat duct. It is a physiologic disturbance associated with excessive secretion of sweat.

*Dyshidrotic Type of Vesicles.*—In the dyshidrotic type (fig. 13) of vesicular lesions, as seen in tinea and in dermatophytide, the cutis shows

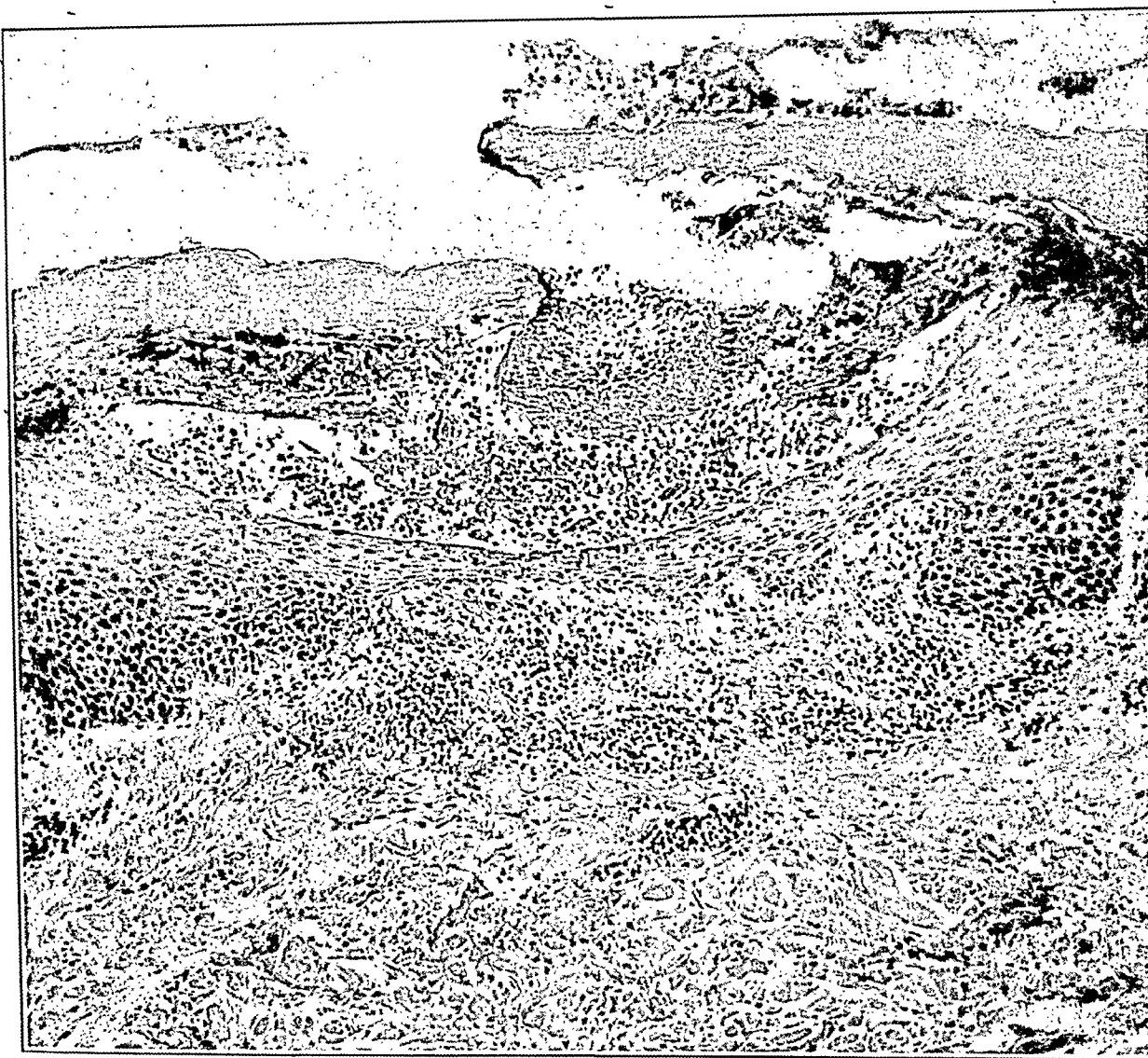


Fig. 14.—Pustular psoriasis. Large intraepidermic vesicle filled with leukocytes. The inflammatory reaction is confined to capillaries and blood vessels in the corresponding portion of the cutis beneath the vesicle. ( $\times 60$ .)

dilatation of the superficial blood vessels. There is a perivascular infiltration of the nonspecific type. Within the epidermis there are one or more large vesicles. These vesicles are located within the intraepidermic portion of the sweat duct. Some elements of the sweat duct system usually appear in each section. The picture is unlike that of contact eczematous dermatitis.

# METASTATIC BASAL CELL EPITHELIOMA

*Report of a Case*

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REFUL search of the literature reveals few cases of metastatic basal cell epithelioma. Most of the cases reported as such later proved to be of the basal-squamous type. There are, however, several which are generally accepted as metastatic basal cell epitheliomas and a number of others which are thought to be possible cases of basal cell epithelioma.

31, Niles<sup>1</sup> reported a case of metastatic basal cell epithelioma which proved to be of the basal-squamous type.<sup>2</sup> A review of the literature in his report included 5 cases of metastatic basal cell epithelioma each reported by Beadles, Janeway and Körbl (case 61) and 4 cases by Finnerud,<sup>3</sup> and 4 cases of possible, but in his opinion not metastatic basal cell epithelioma reported by D. W. Montgomery, Auché and Fordyce, and Marassovich.<sup>4</sup>

35, H. Montgomery<sup>5</sup> pointed out that the 2 cases reported by Beadles had been included in his paper<sup>6</sup> on basal-squamous cell

the New York Skin and Cancer Unit, New York Post-Graduate Medical and Hospital, Columbia University.

es, H. D.: Metastasis of a Basal Cell Epithelioma, Am. J. Cancer 931.

cKee, G. M., and Cipollaro, A. C.: Cutaneous Cancer and Precancer, American Journal of Cancer, 1937.

Beadles, C. F.: Rodent Ulcer, Tr. Path. Soc. London 45:176, 1894.

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Finnerud, C. W.: Metastatic Basal Cell Carcinoma from the Skin: Two Cases, J. A. M. A. 82:775 (March 8) 1924.

Montgomery, D. W.: Report of a Case of Epithelioma of the Skin of the Head and Neck with an Unusual Course of Infection of Lymph Nodes, Ann. Surg. 27:193, 1943.

Reuilh, W., and Auché, B.: De l'ulcus rodens, Ann. de dermat. et syph. 11: 1900.

Fordyce, J. A.: Cancer of the Skin, J. Cutan. Dis. 20:147, 1900.

sch, G.: Beitrag zur Statistik der Carcinome des Gesichtes und der Kopfhaut, Deutsche Ztschr. f. Chir. 104:183, 1910.

Montgomery, H.: Histogenesis of Basal Cell Epithelioma, Radiology

(Footnotes continued on next page)

## SUPPRESSION OF TREPONEMICIDAL ACTION OF ARSENIC WITH 2,3-DIMERCAPTOPROPANOL (BAL)

Report of Clinical Observations in Five Cases

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THE ABILITY of various arsenic compounds to destroy organisms (whether they be invading parasites or the host itself) depends on the combination of the metal with the sulphydryl group of the living cell. This union alters the normal physiology of the cell and results in the eventual death of the organism. Experiment has shown that arsenic and other heavy metals will unite more readily with BAL (2,3-dimercaptopropanol) than with the sulphydryl group of cellular structures,<sup>1</sup> and, therefore, any available arsenic frees itself from the tissues and combines with BAL. It seemed theoretically possible, therefore, that if a supply of BAL were accessible to arsenic injected into a patient who had active lesions of syphilis, the arsenic would be so immobilized by the BAL as to have no effect on the *Treponema pallidum* present, which would, indeed, continue to live and multiply. The following studies of cases seem to substantiate this hypothesis.<sup>2</sup>

### PLAN OF STUDY

In an attempt to evaluate the suppressive action of BAL on the treponemicidal fraction of a trivalent arsenical, 5 patients with acute infectious syphilis with lesions showing organisms on the dark field were treated with BAL and an arsenic compound concomitantly. In 4 cases, six hours before arsenotherapy was instituted, 200 mg. of BAL (10 per cent solution of 2,3-dimercaptopropanol in peanut oil containing 20 per cent benzyl benzoate) was administered intramuscularly and

From the Department of Dermatology and Syphilology, Western Reserve University, Dr. H. N. Cole, Director.<sup>1</sup>

1. Eagle, H.; Magnuson, H. J., and Fleischmann, R.: Clinical Uses of 2,3-Dimercaptopropanol (BAL): I. The Systemic Treatment of Experimental Arsenic Poisoning (Mapharsen, Lewisite, Phenyl Arsenoxide) with BAL, *J. Clin. Investigation* 25:467, 1946.

2. The clinical studies and the many dark field examinations performed in this observation were carried out by the resident staff: Dr. John Bowen, Dr. Burt Held, Dr. Milton Gustafson and Dr. Manly Utterback, on the service of Dr. J. E. Rauschkolb.

tion of her treatment a secondary grade 2 febrile Herxheimer reaction was noted, a grade 1 reaction being observed after the first arsenical injection.

CASE 3.—G. P., a 32 year old Negro, was admitted to the hospital with generalized maculopapular syphiloderm, exhibiting moist papules on the glans penis and prepuce. Dark field examination of the papules revealed numerous *T. pallida*, and the serologic reaction was positive (64 Lund units) in the quantitative test. BAL and oxophenarsine hydrochloride were given at the same time, and within twelve hours repeated dark field examinations did not reveal any organisms. The patient experienced a febrile Herxheimer reaction following administration of oxophenarsine hydrochloride and again following the subsequent administration of penicillin.

CASE 4.—W. C., a 21 year old Negro, was admitted to the ward with seropositive multiple primary lesions of the glans penis. This man was given the same type of treatment as the other patients. The oxophenarsine hydrochloride dose was 0.045 Gm. Numerous *T. pallida* were seen during the first twenty-four hours. However, inadvertently, the fifth injection of BAL was not given at the scheduled time, and within six hours no organisms were seen in the dark field examination. He experienced a grade 1 Herxheimer reaction after the first dose of oxophenarsine hydrochloride and a grade 3 Herxheimer reaction after penicillin therapy was begun.

CASE 5.—F. P., a 31 year old Negro, was admitted to the ward with seropositive primary syphilis of the penis. Observations of the spinal fluid were normal. This man was given 200 mg. of BAL every six hours. With the second injection of BAL, he was given oxophenarsine hydrochloride, 0.045 Gm., which medication was continued daily. Dark field examination of the lesion revealed the presence of organisms until after eighty-five hours of continued treatment. No cutaneous or febrile Herxheimer reactions were observed after oxophenarsine hydrochloride therapy. However, when organisms were no longer seen in dark field examination and treatment with crystalline penicillin was started, a grade 2 Herxheimer reaction was observed. There were no untoward reactions to BAL observed in this patient.

#### COMMENT

In each of these cases BAL was given every six hours, and a dose of somewhat less than the minimal toxic dose was used. Perhaps, had a larger dose of BAL been employed and at more frequent intervals, the period required for the disappearance of *T. pallidum* from the lesions might have been even more prolonged. Case 3 provided a good control, since the BAL, being administered intramuscularly, had little chance to affect the arsenic which, because of its more rapid intravenous route, could act virtually without interference. In this instance the organisms disappeared in less than twelve hours (about what might be expected with ordinary arsenotherapy). In case 4 the omission of a single dose of BAL allowed the arsenic to destroy the organisms of syphilis promptly, as revealed in the dark field examination.

One feature of a secondary febrile Herxheimer reaction seen in each of the cases was striking. Each patient had a febrile reaction when penicillin was administered equal to or greater than the initial one seen after the first injection of oxophenarsine hydrochloride.

## REPORT OF CASE

W. T., a Scottish American housewife aged 39, entered the New York Post-Graduate Skin Clinic Aug. 12, 1935, with a lesion of the scalp near the crown of the head which had developed eight months previously, according to the patient, after a burn from a permanent wave machine. There was no history of cancer or tuberculosis in her family, and the patient's past history was essentially normal. The lesion had always remained about the same size and was not painful, but frequently discharged. A tentative diagnosis of pyodermic ulcer (possibly epithelioma) was made by the examining physician, with the description of a circumscribed matted and crusted purulent area, apparently superimposed on an ulcer. The Wassermann reaction was negative.

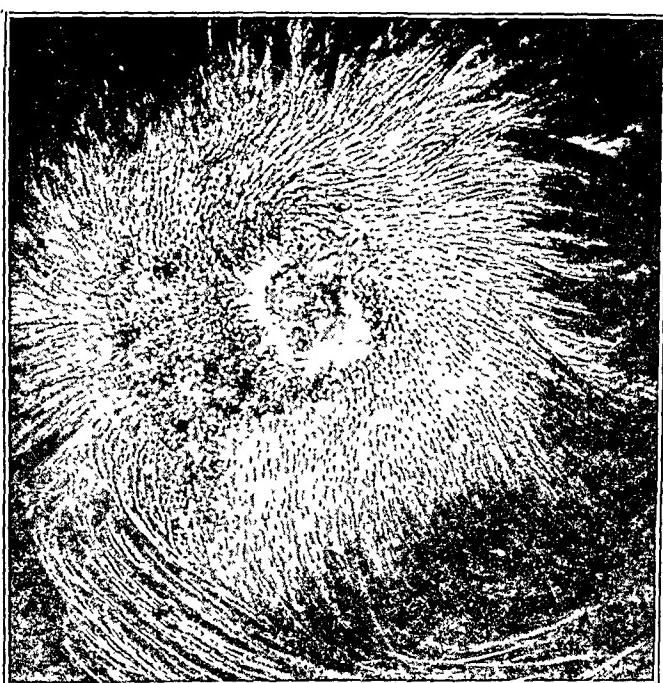


Fig. 1.—Primary basal cell epithelioma of the scalp May 4, 1936.

The patient did not return to the clinic until September 4, when she was treated for a pyodermic ulcer. On March 6, 1936, a biopsy of the lesion of the scalp was made. The pathologic diagnosis, made by Dr. David L. Satenstein, was infiltrating basal cell epithelioma. The entire area was destroyed by curettage and electrodesiccation. The patient attended regularly for dressings. On July 15 the first suggestion of a possible recurrence of the lesion was noted. However, the patient did not attend the clinic from Aug. 3, 1936, to June 7, 1937. On June 30, the recurrent nodule was removed and a specimen for biopsy was taken. A pathologic diagnosis of infiltrating basal cell epithelioma was made. The patient came regularly for dressings until Jan. 10, 1938, when two recurrent nodules were discovered and destroyed by electrodesiccation and curettage. The lesion was dressed regularly, and no evidence of activity was noted in the area of the scar, but on March 4 the attending physician located a robin-egg-sized, slightly movable tumor behind the left ear, which the patient said she had had for six months. The

leukocytes) and 675 red blood cells per cubic millimeter and 250 mg. of protein per hundred cubic centimeters. In repeated examinations, the Wassermann reactions of the spinal fluid were persistently negative and the colloidal gold curves were of the first zone type. During the active phase of the illness the chloride content of the spinal fluid was reduced, fluctuating between 450 and 692 mg. per hundred cubic centimeters. The virus of lymphogranuloma venereum was demonstrated in the spinal fluid, in penile ulcers and in an excised inguinal lymph node. The patient responded well to sulfathiazole, although an elevated cell count and protein content of the spinal fluid were still present five months after the onset of meningitis.

Postmortem identification of the virus of lymphogranuloma venereum was established in the case of a woman hospitalized because of symptoms of meningeal irritation.<sup>10</sup> The patient had suffered from "an inflammatory stricture of the rectum for some time." An emulsion of the patient's brain was injected intracerebrally in white mice and produced the characteristic encephalitis of lymphogranuloma venereum. Furthermore, an antigen prepared from the infected mouse brain elicited positive cutaneous reactions in patients with proved lymphogranuloma venereum.

The virus of lymphogranuloma venereum was shown to be present in the spinal fluid of 1 of 2 men suffering from inguinal lymphadenitis and meningoencephalitis.<sup>11</sup> Both patients had positive Frei reactions. The white cell count of the spinal fluid was elevated in the 2 patients, and in 1 the protein of the fluid reached the remarkable level of 3,570 mg. per hundred cubic centimeters. Seven colloidal gold tests were performed, and all the curves had the first zone deviation. The Wassermann reactions of the spinal fluid were negative in both cases.

Recently, meningoencephalitis was observed in a young white man shortly after an attack of inguinal lymphadenitis.<sup>12</sup> The patient had positive Frei reactions to the tests, and the reactions in the complement fixation tests of the blood and spinal fluid for lymphogranuloma venereum were also positive. Efforts to demonstrate the virus by inoculation of animals with spinal fluid, blood and lymph node were unsuccessful. The spinal fluid was repeatedly abnormal, the white cells ranging between 4 and 270 per cubic millimeter and the protein between 38 and 156 mg. per hundred cubic centimeters. The colloidal gold curve was of the first zone type, but the Wassermann reaction of the fluid was persistently negative. A single determination of chloride

10. D'Aunoy, R., and von Haam, E.: Venereal Lymphogranuloma, Arch. Path. 27:1032 (June) 1939.

11. Zarafonetis, C. J. D.: Meningoencephalitis in Lymphogranuloma Venereum, New England J. Med. 230:567, 1944.

12. Scott, D. W., Jr.: Recurrent Meningoencephalitis Due to the Virus of Lymphogranuloma Venereum, Arch. Int. Med. 76:174 (Sept.) 1945.

mass had shown no increase in size during the last three months, was not painful and did not discharge. Three days later, on March 7, a specimen for biopsy was taken. A pathologic diagnosis of infiltrating disseminated basal cell epithelioma was made.

On April 8, the patient was referred to the tumor clinic for consultation and treatment. On April 14, Dr. George F. MacFee made a diagnosis of epithelioma of the scalp with metastasis to the left postauricular lymph node. Dr. D. S. D. Jessup examined the biopsy sections which had previously been made in the skin clinic and concurred in the diagnosis of basal cell epithelioma. A week later, Dr. Jessup reported on the biopsy specimen taken by the tumor clinic from the scalp: basal cell epithelioma of the scalp with growth of basal cells in nests extending through the depth of the section.

The patient was admitted to the New York Post-Graduate Hospital April 24 for radical excision with plastic repair and skin graft. At the operation, on April 25, which was performed by Dr. Alexander Zimany with the patient under ether anesthesia and lasted two and one-half hours, excision and plastic reconstruction with a Thiersch graft from the left thigh were accomplished.



Fig. 2.—Metastatic basal cell lesion of the postauricular lymph node.

Recently Dr. Wilbur Sachs reexamined the biopsy sections of March 6, 1936, June 30, 1937, and March 7, 1938, and diagnosed all three as basal cell epithelioma. There was no evidence of the basal-squamous or mixed type, or of the more serious prickle cell or anaplastic epithelioma. He also made the following histologic descriptions.

*Biopsy of March 6, 1936.*—Extending down from the epidermis to the bottom of the section was a large epithelial mass arranged in lobes, lobules, strands and bands. About the mass was a considerable increase in connective tissue (fibrosis) with a diffuse fibroblastic cell infiltration. In other areas, chiefly at the periphery of the lesion, was a dense cellular infiltration composed chiefly of plasma cells with some small round cells. The epidermis was moderately acanthotic but otherwise showed no important change. At the other end of the section, the epidermis was entirely missing over the underlying mass.

The mass itself was composed of basal cells with large, deeply stained, round and oval nuclei, and a slight amount of cytoplasm, but nowhere could the outlines of the cells be seen. There were no prickles, whorls or pearls. There was no pigment and the palisade layer was missing throughout.

chloride), limits of 700 to 750, with an average of 726 mg.; total protein, limits of 15 to 45, with an average of 28 mg., and sugar, limits of 50 to 80, with an average of 65 mg.

### RESULTS

The observations in the 25 cases are detailed in the table. The most significantly abnormal spinal fluid was seen in a patient (case 19) who had received adequate treatment for presumably latent syphilis. The patient had no symptoms or signs of disease of the central nervous

*Observations of the Spinal Fluid in Twenty-Five Cases of Lymphogranuloma Venereum*

Case No.	STS *	Syphilis	Results of Examinations of Spinal Fluid						
			Wassermann Reaction	Mono-nuclear Cells	Pandy Reaction	Protein, Mg.	Chloride, Mg.	Sugar, Mg.	Colloidal Gold Curve
1	Negative	Absent	Negative	0	0	47	660	54	0000000000
2	Negative	Absent	Negative	0	0	19	...	..	0000000000
3	Negative	Absent	Negative	0	0	23	...	76	0000000000
4	Negative	Absent	Negative	0	0	27	...	..	0000000000
5	Negative	Absent	Negative	0	0	14	701	47	0000000000
6	Negative	Absent	Negative	0	0	39	...	..	0000000000
7	Negative	Absent	Negative	0	0	14	708	53	0000000000
8	Negative	Absent	Negative	0	0	10	693	60	0000000000
9	Negative	Absent	Negative	0	0	28	729	57	0000000000
10	Negative	Absent	Negative	0	Trace	27	643	57	1121110000
11	Negative	Absent	Negative	0	0	26	...	67	0000000000
12	Negative	Absent	Negative	0	0	57	685	66	0000000000
13	Negative	Absent	Negative	0	0	..	748	74	0000000000
14	Negative	Latent	Negative	0	0	27	660	78	0000000000
15	Negative	Latent	Negative	0	0	27	546	65	1122110000
16	Positive	Spp †	Negative	1	0	16	...	..	0000000000
17	Positive	Sec ‡	Negative	0	0	42	...	..	0000000000
18	Doubtful	Latent	Negative	2	0	48	...	..	0000000000
19	Positive	Latent	Positive	0	0	..	701	57	5543321000
20	Positive	Latent	Positive	10	+	132	...	..	4443200000
21	Negative	Absent	Negative	1	0	..	...	..	0000000000
22	Negative	Absent	Negative	0	0	..	...	..	0000000000
23	Negative	Absent	Negative	2	0	42	...	..	0000000000
24	Negative	Absent	Negative	1	0	44	...	..	0000000000
25	Negative	Absent	Negative	0	0	72.9	...	..	0000000000
						19.2	...	..	0000000000

\* STS stands for serologic test for syphilis.

† Spp stands for seropositive primary syphilis.

‡ Sec stands for secondary syphilis.

system. The Kahn and Wassermann reactions of the blood were strongly positive, and the spinal fluid initially yielded a positive Wassermann reaction and an abnormal colloidal gold curve. After completion of the course of sulfonamide drugs and nineteen days after the first lumbar puncture, reexamination of the spinal fluid showed not only the positive Wassermann reaction, and abnormal gold curve but also mild pleocytosis and considerable increase of the total protein.

In the remaining 24 cases, the Wassermann reaction of the spinal fluid was negative and the cell count and reaction to the Pandy test were normal. The total protein was moderately increased in 2 additional patients (cases 12 and 24) to 57 and 72.9 mg. per hundred cubic



Fig. 3.—Photomicrograph of pathologic section from the lesion of the scalp.  
( $\times 49$  [approximately].)

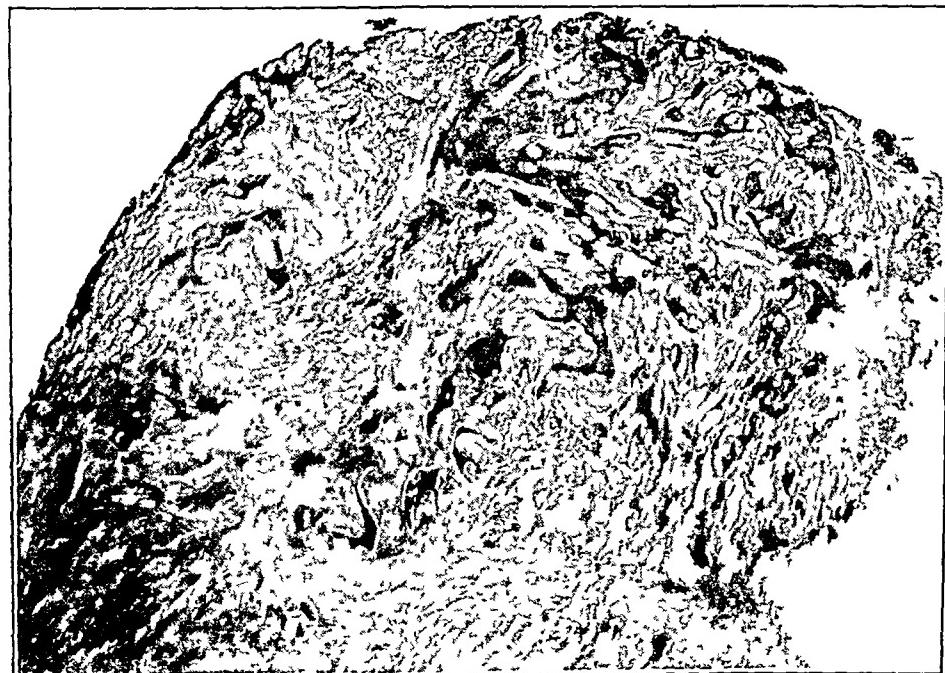


Fig. 4.—Photomicrograph of pathologic section from the lymph node lesion.  
( $\times 49$  [approximately].)

Furthermore, biologic false positive Wassermann reactions of the spinal fluid have been noted in various diseases, as bacterial meningitis and aseptic lymphocytic meningitis.<sup>16</sup> It is important, in this connection, to point out that in all the proved and presumptive cases of lymphogranuloma meningoencephalitis there were negative Wassermann reactions of the spinal fluid. Also, not a single biologic false positive Wassermann reaction was observed in the spinal fluid of my 25 patients. The positive Wassermann reaction in case 19 of my series was attributed to a syphilitic infection which long antedated the infection caused by the virus of lymphogranuloma venereum. These observations are in complete agreement with those of others,<sup>17</sup> except the observations of Kitigawa.<sup>4</sup> However, there is sufficient evidence in Kitigawa's paper to justify the assumption that his patients were suffering from a concomitant syphilitic infection, which explained the positive Wassermann or Meinicke reactions of the spinal fluid.

The clinical picture of lymphogranuloma meningoencephalitis resembles closely that of acute syphilitic meningitis. Moreover, the changes in the spinal fluid are strikingly similar so far as the increase of cells and protein and the abnormalities of the colloidal gold curve are concerned. When syphilis and lymphogranuloma venereum coexist this similarity might lead to confusion in the diagnosis of a complicating meningitic syndrome. If facilities for virus studies are not available, decision as to the cause of the meningitis would depend on the results of Wassermann tests of the spinal fluid, since the Wassermann reaction has been consistently negative in all recorded cases of lymphogranuloma meningoencephalitis.

#### SUMMARY

The spinal fluid of 25 patients with acute lymphogranuloma venereum showed no cytologic or chemical alterations that could be considered significant of asymptomatic virus invasion of the central nervous system. Biologic false positive Wassermann reactions of the spinal fluid did not occur in the 25 cases of acute lymphogranuloma venereum or in the published cases of lymphogranuloma meningoencephalitis. The clinical picture and the observations of the spinal fluid in acute syphilitic meningitis and in lymphogranuloma meningoencephalitis are strikingly similar, with the exception of the Wassermann reaction of the spinal fluid which is persistently negative in lymphogranuloma meningoencephalitis.

32 East Thirty-ninth Street.

16. Scott, V.; Reynolds, F. W., and Mohr, C. F.: Biologic False Positive Spinal Fluid Wassermann Reactions Associated with Meningitis, Am. J. Syph., Gonor. & Ven. Dis. 28:431, 1944.

17. Midana and Vercellino.<sup>1a</sup> Mollaret and Vieuchange.<sup>1b</sup> Von Haam and D'Aunoy.<sup>2a</sup> Koschucharoff.<sup>2b</sup> Ravaut and Scheikevitch.<sup>2c</sup> Cruz.<sup>2d</sup>

In some areas, especially where the fibrosis was greatest, the cells which composed the mass were spindle shaped.

*Biopsy of March 7, 1938.*—Throughout the section there was an epithelial mass arranged in strands and bands. About the mass was a pronounced increase in connective tissue (fibrosis) with a diffuse fibroblastic cell infiltration. There was no epidermis present.

The mass was composed of basal cells with deeply stained, oval and round nuclei with a slight amount of cytoplasm, but nowhere could the outlines of the cells be seen. There were no prickles, whorls or pearls. There was no pigment and the palisade layer was missing throughout. In some areas the cells were spindle shaped.

The patient was seen at regular intervals until June 12, 1941, which was the date of her last visit. There was no evidence of recurrence at any time during that period, and results were excellent. The patient, however, has failed to return for further examination.

Photographs of the lesions and photomicrographs of the biopsy sections are shown.

#### COMMENT

Metastasis is the shifting or transplanting of a disease from one organ to another, usually via the lymph channels. The fact that basal cell epitheliomas generally do not metastasize has been noted in numerous papers and textbooks. H. Montgomery,<sup>10</sup> Sohrweide,<sup>11</sup> MacKee and Cipollaro<sup>2</sup> and Andrews<sup>12</sup> have all stated that often the metastatic basal cell epithelioma proves on careful study to have some features of the mixed type or the squamous type in the original or in the secondary lesion and that 15 to 20 per cent of the basal cell epitheliomas which are diagnosed clinically prove on microscopic examination to be basal squamous or squamous cell epithelioma.

MacLeod and Muende<sup>13</sup> considered basal cell epitheliomas as never metastasizing and referred to them as locally malignant.

Cade<sup>14</sup> noted in basal cell epitheliomas that secondary nodules are sometimes seen in the vicinity of the main lesion following the anatomic course of the lymphatics of the skin, indicating that the neoplastic cells directly invade the lymph vessels. However, he pointed out that involvement of the regional lymph node is most exceptional but actually does occur, for in a series of 183 cases of typical basal cell epithelioma in thirteen years, he observed only 1 case.

10. Montgomery (footnotes 5 and 6).

11. Sohrweide, A. W.: The Basal Cell Epithelioma: A Resumé, *M. Times*, New York **64**;184, 1936.

12. Andrews, G. C.: Diseases of the Skin for Practitioners and Students, Philadelphia, W. B. Saunders Company, 1939.

13. MacLeod, J. M. H., and Muende, I.: Practical Handbook of the Pathology of the Skin, New York, Paul B. Hoeber, Inc., 1940.

14. Cade, S.: Malignant Disease and Its Treatment by Radium, Bristol, John Wright & Sons, Ltd., 1940.

injected intramuscularly, 50,000 units in aqueous solution every three hours. One week later some improvement could be seen. The discharge had ceased; the lesion had become flatter, and the tenderness had decreased. By February 13 the patient had received 10,000,000 units of penicillin. Considerable improvement was noted. There was neither discharge nor tenderness on pressure. The lesion had become smaller, flatter and pale pink. There were no untoward reactions from penicillin. No local treatment had been given during the course of penicillin. The lesion had been kept covered with a sterile dressing.

After the completion of the treatment with penicillin radiotherapy was begun. Treatments with roentgen rays were given on February 13, 14, 17, 19, 21, 24, 26 and 28, a total of eight treatments. A current of 200 kilovolts was used, with a

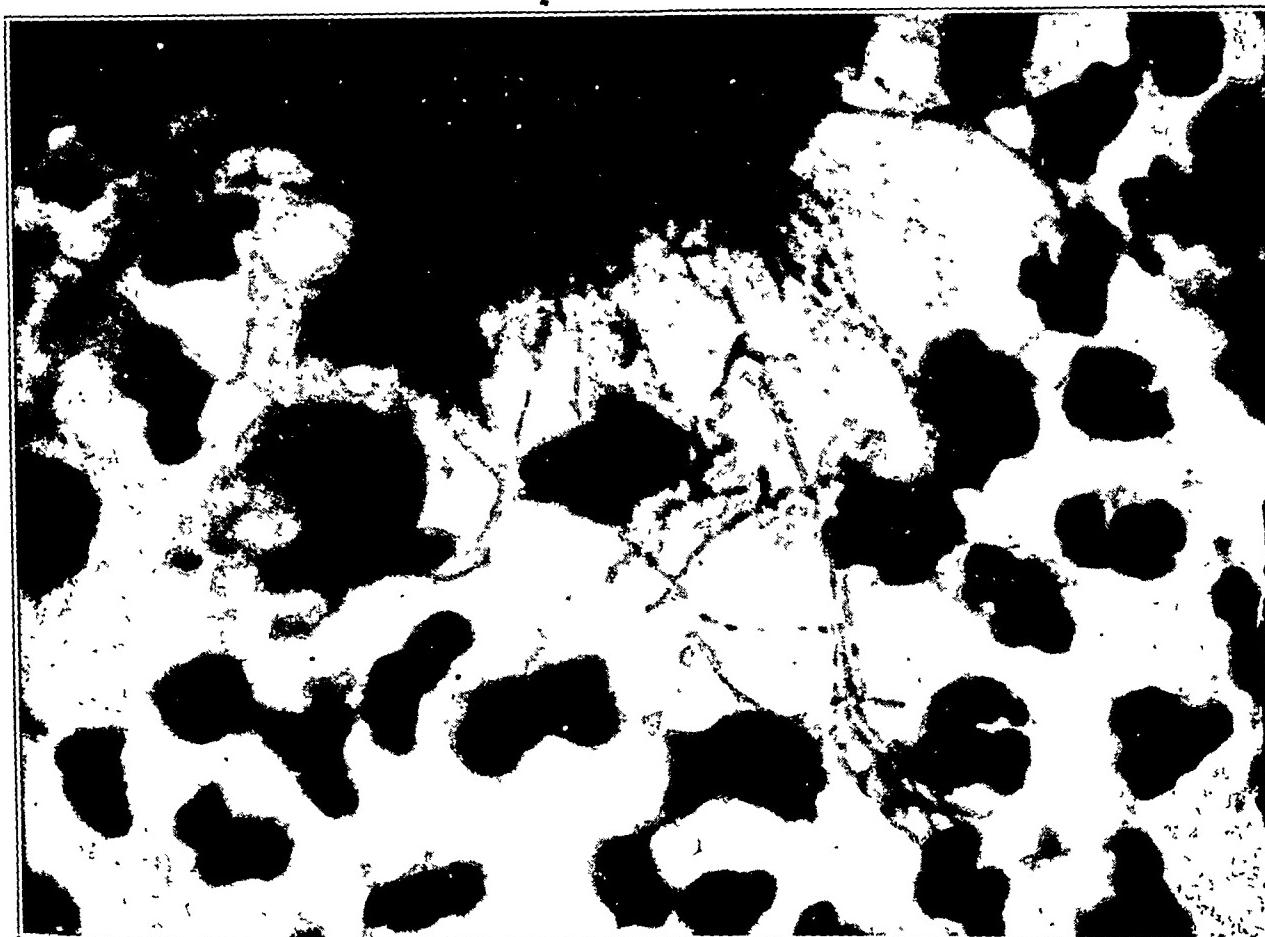


Fig. 4.—Actinomycotic granule in pus (Gram's stain,  $\times 2,000$ , oil immersion objective), showing the fine-branched and beaded fungous filaments.

filter of 0.5 mm. of copper and 1 mm. of aluminum. The focal skin distance was 50 cm. The size of the exposed area was 8 by 10 cm. during the first five treatments and 6 by 8 cm. during the last three treatments. During the course of radiation therapy, the lesion was probed several times and the material obtained was cultured three times for actinomycetes, with negative results. The patient was discharged from the hospital on February 24. On that day she began to take saturated solution of potassium iodide by mouth, beginning with 3 drops three times daily and increasing the dose by 1 drop daily. On April 29, three and one-half months after the beginning of the treatment, the formerly affected area did not show any signs of activity. There was a linear pinkish scar of a firm consistency and without sinuses

Horsley<sup>15</sup> tried to give an explanation for the lack of metastases in the basal cell epithelioma as compared with the prickle cell type, which metastasizes frequently. He assumed that the basal cells are transported to tissues at a distance from the original lesion but perish because some substance makes their growth in the location impossible. Apparently, in tissues in the immediate neighborhood of the basal cell epithelioma the resistance is weakened or abolished.

Holtzman and Bolker<sup>16</sup> attributed the absence of metastasis in basal cell epithelioma, in spite of the presence of neoplastic tissue in the lymph capillaries, to the inherent cohesion (or continuity) of the protoplasm of these cells.

The case of W. T. apparently is one of the rare instances of a metastatic basal cell epithelioma, for no histologic evidence appears in any of the biopsy material taken that other than basal cell progeny occurred, in either the lesions of the scalp or the lymph node involvement. Sections through the entire lymph node revealed nothing which was reported as mixed, spindle or squamous in types.

It may be that basal cell epitheliomas metastasize as such more frequently, but since such a metastasis is considered unusual it is likely to be overlooked. It is certainly advisable to make a histologic examination of every cancerous lesion and to consider all types as potentially dangerous.

#### SUMMARY

The case is presented of a patient who had a basal cell epithelioma on the scalp which metastasized to the postauricular lymph node. Since histologic examination of the lesions of the scalp and lymph node revealed basal cell epithelioma, the case is considered to be of metastatic basal cell epithelioma.

105 East Fifty-Third Street.

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15. Horsley, J. S.: Basal Cell Carcinoma of the Skin, *S. Clin. North America* **2**:1247, 1922.

16. Holtzman, I., and Bolker, H.: Basal Cell Epithelioma: A Concept of Its Histogenesis, *Am. J. Roentgenol.* **47**:463, 1942.

## Editorials

### INTERNATIONAL DERMATOLOGIC CONGRESS

The Tenth International Congress of Dermatology and Syphilology was to have been held in New York in September 1940, but was postponed because of the war. It has been suggested that the Congress be called to meet in this country in 1950. The success of the Fifth International Congress of Pediatrics held in New York in July of this year, which attracted 2,200 registrants, of whom approximately one fourth were from abroad, would indicate that a dermatologic congress would be equally well received. It will require more time, however, to prepare for such a meeting now than was needed in 1940, because many of the European dermatologic societies are disorganized or not functioning.

An international dermatologic congress is a gathering of men and women from all over the world who are interested primarily in diseases of the skin and allied conditions. Such a meeting has many ramifications. It, of course, affords a stimulus to scientific effort. The dissemination of recently established scientific data, the evaluation of new remedies, the clarification of the nosology of new diseases and the appraisal of recent developments of older ones, and the demonstrations of technics—both therapeutic and diagnostic—are some of the fundamental reasons for holding a congress. An international meeting, however, not only disseminates scientific information; it exerts social, economic and personal influences as well.

The recent war is one of the factors which has advanced American dermatology to a position of leadership. It is, therefore, the privilege of the dermatologists of this country to accept the position with humility and generosity—generosity in giving to our colleagues from abroad knowledge and inspiration, just as they gave to those Americans who went to European clinics during the past generation when adequate graduate instruction was not obtainable in America. Although the names and faces in the clinics have changed during the years, the spirit of dermatology the world over has not, and it is now American dermatologists' turn to be the hosts. American dermatologists will do so with enthusiasm, for the bonds of camaraderie, cooperation and friendliness among American dermatologists—always strong—have been strengthened even more in recent years.

As persons concerned with saving mankind rather than destroying it, as men and women interested primarily in giving rather than accept-

## PENICILLIN IN THE TREATMENT OF EXPERIMENTAL SYPHILIS OF RABBITS

### II. The Synergistic or Additive Activity of Penicillin, Oxophenarsine Hydrochloride and Bismuth and Potassium Tartrate

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With the Technical Assistance of ANNA M. RULE

PHILADELPHIA

THAT the simultaneous administration of penicillin by intermittent intramuscular injection over a period of eight days with daily intravenous injections of oxophenarsine hydrochloride in doses of 40 mg. is more effective than penicillin alone in the treatment of early syphilis of adults appears to be well substantiated. The therapeutic effects of the two compounds given simultaneously may be additive, but Eagle, Magnuson and Fleischman<sup>1</sup> have reported that they were apparently synergistic in the treatment of acute syphilitic orchitis of rabbits. For example, these investigators found that when sodium penicillin was injected intramuscularly five times daily at four hour intervals for four days the total minimal curative dose was approximately 8,000 units per kilogram; the concurrent administration of oxophenarsine hydrochloride in subcurative doses of 0.4 mg. per kilogram daily for four days by intravenous injection, however, reduced the total minimal curative dose of penicillin to approximately 1,000 units per kilogram.

As herein reported, these observations have been confirmed. We have also found similar synergistic or additive effects by the simultaneous administration of penicillin and bismuth and potassium tartrate in oil by intramuscular injection in the treatment of acute syphilitic orchitis of rabbits. In the circumstances, it now appears that the optimum therapy for human syphilis may consist of the simultaneous administration of penicillin and oxophenarsine hydrochloride, penicillin and bismuth and potassium tartrate or a combination of all three compounds.

#### METHODS AND MATERIALS

In our experiments all rabbits were inoculated intratesticularly with the Nichols-Hough strain of *Treponema pallidum*. Acute orchitis developed in all,

From the Research Institute of Cutaneous Medicine.

1. Eagle, H.; Magnuson, H. J., and Fleischman, R.: The Synergistic Action of Penicillin and Mapharsen (Oxophenarsine Hydrochloride) in the Treatment of Experimental Syphilis, *J. Ven. Dis. Inform.* 27:3 (Jan.) 1946.

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## HISTOPLASMOSIS

Cutaneous and Mucomembranous Lesions, Mycologic and Pathologic Observations

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**H**ISTOPLASMOSIS should be of interest to dermatologists because cutaneous or mucomembranous lesions have been observed in one half of the reported cases. The literature has been reviewed, disclosing reports on 88 patients with the disease. In 1945, Parsons and Zarafonetis<sup>1</sup> referred to 71 of these cases. We have read of 17 more<sup>2</sup>

From the Departments of Dermatology, Bacteriology and Pathology, University of California Medical School.

Read at the Sixty-Sixth Annual Meeting of the American Dermatological Association, Inc., Hot Springs, Va., June 12, 1946.

1. Parsons, R. J., and Zarafonetis, C. J. D.: Histoplasmosis in Man: Report of Seven Cases and a Review of Seventy-One Cases, *Arch. Int. Med.* **75**:1 (Jan.) 1945.

2. (a) Strong, R. P.: A Study of Some Tropical Ulcerations of the Skin with Particular Reference to Their Etiology, *Philippine J. Sc.* **1**:91 (Jan.) 1906. (b) Alonso, J. M., and Cancelo Freijo, J.: Histoplasmosis of Darling: First Observations of a Patient in Uruguay; Clinical Cure with Sulfadiazine, *Arch. urug. de med., cir. y especialid.* **24**:193 (March) 1944. (c) Balina, P.; Herrera, J. A.; Bosq, P., and Negroni, P.: Tercer caso Argentino de histoplasmosis: Beneficio de la sulfamidoterapia, *Rev. argent. dermatosif.* **27**:453 (Sept.) 1943. (d) Boltjes, B.: Histoplasmosis: Report of a Case with Brief Review of the Literature, *J. Kansas M. Soc.* **44**:226 (July) 1943. (e) Christie, A., and Peterson, J. C.: Pulmonary Calcification in Negative Reactors to Tuberculin, *Am. J. Pub. Health* **35**:1131 (Nov.) 1945. (f) German, W. M.; Ashmun, S., and Dille, C. E.: Histoplasmosis: Case Report, *Am. J. Clin. Path.* **13**:12 (Jan.) 1943. (g) Kemper, J. W., and Bloom, H. J.: Histoplasmosis: Report of a Case, *J. Oral Surg.* **2**:167 (April) 1944. (h) Martin, W. P., and Silber, B.: Histoplasmosis of Darling (Reticulo-endothelial Cytomycosis): Case Report, *Am. J. Clin. Path.* **14**:119 (Feb.) 1944. (i) McLeod, J. H.; Emmons, C. W.; Ross, S., and Burke, F. G.: Histoplas-

(Footnote continued on next page)

with strongly positive results on dark field examinations about five to six weeks thereafter, when treatment was instituted. Dark field examinations were then made once a day for three days in succession and thereafter once a week over a total period of seventy days. At the expiration of this time the popliteal lymph nodes of all treated animals were inoculated into the testicles of fresh animals, which were kept under observation for a minimum of four months, when the results were evaluated.

The penicillin employed was a commercial amorphous sodium salt with an assay potency of 544 units per milligram, containing 88 per cent penicillin G, supplied by the Commercial Solvents Corporation (lot no. 45072102).

Aqueous solutions of the compound were freshly prepared as required in sterile isotonic solution of sodium chloride containing 10,000 units per cubic centimeter. Suspensions were prepared in sterile peanut oil and 3 per cent beeswax containing 10,000 units per cubic centimeter and kept at 4 C.

Solutions of oxophenarsine hydrochloride were freshly prepared as required in sterile distilled water. A suspension of the compound was also prepared in sterile peanut oil and 3 per cent beeswax containing 5 mg. per cubic centimeter and kept at room temperature.

Bismuth and potassium tartrate in oil with butacaine sulfate (Abbott Laboratories) was employed. As dispensed, this preparation contained 0.1 Gm. per cubic centimeter; for use it was diluted with sterile peanut oil and 3 per cent beeswax to contain 0.010 Gm. per cubic centimeter.

In some experiments oxophenarsine hydrochloride in peanut oil and beeswax and penicillin in peanut oil and beeswax were mixed immediately before intramuscular injection; the same method was employed in preparing mixtures of penicillin in peanut oil and beeswax and of bismuth and potassium tartrate in oil diluted with peanut oil and beeswax. In this connection we have observed that assays of both mixtures kept at 4 C. every three days over a period of four weeks showed a loss of no more than about 15 per cent of penicillin at the expiration of this period. It would appear, therefore, that the penicillin employed in peanut oil and beeswax remained rather stable in mixtures with oxophenarsine hydrochloride and in mixtures with bismuth and potassium tartrate in peanut oil and beeswax over a period of four weeks at least when kept at a low temperature.

All doses of penicillin were given in terms of units per kilogram of weight by intramuscular injection in the thighs, followed by brief massage. So far as we could judge clinically intramuscular injections of mixtures of penicillin and oxophenarsine hydrochloride and of mixtures of penicillin and bismuth and potassium tartrate in peanut oil and beeswax were well borne, with practically no more local reactions at the sites of injection than produced by penicillin or bismuth and potassium tartrate alone.

#### RESULTS OBSERVED

*Synergistic Activity of Single Doses of Penicillin and Oxophenarsine Hydrochloride.*—As previously reported,<sup>2</sup> single intramuscular injections of 100,000 units of penicillin in isotonic solution of sodium chloride per kilogram of weight did not effect the complete or biologic cure of

2. Kolmer, J. A., and Rule, A. M.: Penicillin in the Treatment of Experimental Syphilis of Rabbits: I. The Therapeutic Activity of Penicillin in Single and Multiple Doses in Isotonic Solution of Sodium Chloride and Peanut Oil-Beeswax by Intramuscular Injection, Arch. Dermat. & Syph. 55:741 (June) 1947.

## HISTORICAL REVIEW

Darling observed the first cases of histoplasmosis in Panama in 1906,<sup>3h</sup> 1908<sup>3i</sup> and 1909<sup>4</sup> while searching for examples of visceral and cutaneous leishmaniasis. Strong<sup>2a</sup> saw a patient in the Philippine Islands at about the same time with an abscess which may have been due to the same or to a similar organism. Darling named the causative agent *Histoplasma capsulatum* and stated the belief that it was a protozoon, because of its similarity to the organism causing kala-azar. DeMonbreun<sup>5</sup> in 1934 furnished definite proof that the organism is a fungus. Its habitat in nature, modes of transmission and portal of entry into the human body have as yet not been determined. No new cases of histoplasmosis were recognized from 1909 until 1926, when 2 were reported. Since then the disease has been observed with increasing frequency.

## EPIDEMIOLOGY

The sources of infection and the modes of transmission of *H. capsulatum*, as already stated, have not as yet been elucidated. We are

4:378 (Sept.) 1943. (y) Beamer, P. R.; Smith, E. R., and Barnett, H. L.: Histoplasmosis, J. Pediat. 24:270 (March) 1944. (z) Negroni, P.: Estudio micológico del primer caso sud-americano de histoplasmosis, Argent. Inst. Bact. 9:239, 1939-1940. (a') Hansmann, G. H., and Schenken, J. R.: A Unique Infection in Man with a New Yeast-like Organism, Am. J. Path. 9:925 (Nov.) 1935. (b') Parsons, cited by Parsons and Zarafonetis.<sup>1</sup> (c') Steiner, P., cited by Parsons and Zarafonetis (case G).<sup>1</sup> (d') Stingily, cited by Parsons and Zarafonetis (case H).<sup>1</sup> (e') Agress, H., and Gray, S. H.: Histoplasmosis and Reticuloendothelial Hyperplasia, Am. J. Dis. Child. 57:573 (March) 1939. (f') Brown, A. E.; Havens, F. Z., and Magath, T. B.: Histoplasmosis: Report of a Case, Proc. Staff Meet., Mayo Clin. 15:812 (Dec. 18) 1940. (g') Henderson, R. C.; Pinkerton, H., and Moore, L. T.: *Histoplasma Capsulatum* as a Cause of Chronic Ulcerative Enteritis, J. A. M. A. 118:885 (March 14) 1942 (h') Meleney, H. E.: Histoplasmosis (Reticulo-Endothelial Cytomycosis): A Review with Mention of Thirteen Unpublished Cases, Am. J. Trop. Med. 20:603 (July) 1940. (i') Simson, F. W., and Barnetson, J.: Histoplasmosis: Report of a Case, J. Path. & Bact. 54:299 (July) 1942. (j') Van Pernis, P. A.; Benson, M. E., and Holinger, P. H.: Specific Cutaneous Reactions with Histoplasmosis: Preliminary Report of Another Case, J. A. M. A. 117:436 (Aug. 9) 1941. (k') Williams, R. H., and Cromartie, W. J.: Histoplasmosis: Report of a Case, Ann. Int. Med. 13:2166 (May) 1940. (l') Rhodes, P. H.; Conant, N. F., and Glesne, L. R. B.: Histoplasmosis: Report of a Case in Three Months Old Infant, J. Pediat. 18:235 (Feb.) 1941. (m') Moore, M., and Blache, J. O., cited by Meleney.<sup>3h'</sup> (n') Hild, J. R.: Histoplasmosis in Infancy, Am. J. Dis. Child. 63:131 (Jan.) 1942. (o') Mantell, F. J.; Troy, T. S., and Kendall, W. S., cited by Meleney.<sup>3h'</sup>

4. Darling, S. T.: The Morphology of the Parasite (*Histoplasma Capsulatum*) and the Lesions of Histoplasmosis, a Fatal Disease of Tropical America, J. Exper. Med. 11:515, 1909.

5. DeMonbreun, W. A.: The Cultivation and Cultural Characteristics of Darling's *Histoplasma Capsulatum*, Am. J. Trop. Med. 14:93 (March) 1934.

acute syphilitic orchitis of rabbits. As shown in table 1, however, single doses of penicillin in isotonic solution of sodium chloride as small as 10,000 units per kilogram by intramuscular injection were completely curative when administered at the same time as 1.0 mg. of oxophenarsine hydrochloride per kilogram by intravenous injection. This single dose of oxophenarsine hydrochloride alone resulted in temporarily negative results on dark field examinations for *T. pallidum* but was not curative, since the single minimal curative dose of the compound is about 8.0 to 10.0 mg. per kilogram. In the circumstances, the simultaneous injection of one-eighth to one-tenth the minimal single curative dose of oxophenarsine hydrochloride by intravenous injection reduced the single minimal curative dose of penicillin by intramuscular injection from over 100,000 units to probably less than 10,000 units per kilogram of weight.

As previously reported,<sup>2</sup> the single minimal curative dose of penicillin in peanut oil and beeswax was approximately 10,000 units per kilogram of weight in the treatment of acute syphilitic orchitis of rabbits. As shown in table 2, the intramuscular injection of 2,000 units of penicillin along with 2.0 mg. of oxophenarsine hydrochloride in peanut oil and beeswax resulted in biologic cure. This dose of oxophenarsine hydrochloride alone produced temporarily negative results on dark field examinations without biologic cure. The minimal single curative dose of oxophenarsine hydrochloride in peanut oil and beeswax is approximately 20.0 mg. per kilogram. In the circumstances, it appears that the simultaneous intramuscular injection of approximately one-tenth the minimal single dose of oxophenarsine hydrochloride in peanut oil and beeswax reduced the minimal single dose of penicillin in this vehicle from 10,000 units to probably less than 2,000 units per kilogram of weight.

*Synergistic Activity of Multiple Doses of Penicillin and Oxophenarsine Hydrochloride.*—As previously reported,<sup>2</sup> the minimal curative dose of penicillin in isotonic solution of sodium chloride by intramuscular injection was approximately 1,000 units per kilogram when given twice daily for eight days in succession, totaling 16,000 units. As shown in table 3, however, a dose of 250 units of penicillin per kilogram administered intramuscularly twice daily for eight days in succession, totaling 4,000 units, was completely curative when administered along with 0.2 mg. of oxophenarsine hydrochloride per kilogram by intravenous injection once a day for eight days in succession, totaling 1.6 mg. This dose of oxophenarsine hydrochloride alone produced temporarily negative results on dark field examinations but was not curative. The total minimal curative dose of oxophenarsine hydrochloride by this method of administration was not determined, but in the circumstances the minimal total curative dose of 16,000 units of penicillin in isotonic solution of sodium chloride was reduced to 4,000 units or less per kilo-

benign forms of the disease has been the subject of considerable speculation recently on the part of several investigators. That histoplasmosis might be the cause of pulmonary calcifications in persons with negative tuberculin reactions was first suggested by Smith<sup>9</sup> in 1943. Christie and Peterson<sup>2e</sup> discussed controversial questions on the relationship of histoplasmosis to the occurrence of pulmonary calcification in those with negative reactions to tuberculin. They exhaustively summarized the observations of previous investigators, which, amplified by their own, clearly indicate ". . . with monotonous regularity the fact that there is in certain sections of the United States a prevalence of pulmonary calcification far beyond what can be explained on the basis of tuberculosis as revealed by tuberculin testing." Christie and Peterson were the first to employ histoplasmin in an intradermal sensitivity test in an appreciable number of patients. During the progress of their studies they tested 181 Tennessee children and observed that 73.5 per cent reacted to histoplasmin. Many of the children who showed a positive reaction had pulmonary calcification and negative reactions to tuberculin. Palmer,<sup>10</sup> following the suggestion of Christie and Peterson, included histoplasmin tests in addition to tuberculin tests and roentgenograms of the chest in his nationwide study of early tuberculosis in student nurses. Of 3,105 nurses studied in Detroit, Kansas City (Missouri and Kansas), Minneapolis and Philadelphia, 22.9 per cent showed definite positive reactions to histoplasmin. The percentage of positive reactions varied considerably in the different cities. Palmer reported that of the nurses reacting only to tuberculin, 10.4 per cent showed calcifications, while of those reacting to histoplasmin, 31.1 per cent showed this process. In the group in which the reactions to both tuberculin and histoplasmin tests were positive, 34.1 per cent showed calcifications. In the large group of 2,141 nurses in which no reactions to either of the antigens occurred, only 1.2 per cent showed pulmonary calcification. In a more recent paper, Palmer<sup>10b</sup> reported on the geographic distribution of sensitivity to histoplasmin in the United States. A group of 8,141 nurses with lifetime residences representing every state and the District of Columbia were tested, and 20.9 per cent of this widespread group reacted to histoplasmin. The region in which the highest percentage of positive reactors occurred includes Tennessee, Kentucky, Arkansas, Missouri, Indiana and parts of Ohio, Illinois, Kansas and Louisiana. This extensive survey of sensitivity to histoplasmin conducted by Palmer shows that the incidence of positive

9. Smith, C. E.: Coccidioidomycosis, *M. Clin. North America* **27**:790 (May) 1943.

10. (a) Palmer, C. E.: Nontuberculous Pulmonary Calcification and Sensitivity to Histoplasmin, *Pub. Health Rep.* **60**:513 (May 11) 1945; (b) Geographic Differences in Sensitivity to Histoplasmin Among Student Nurses, *ibid.* **61**:475, 1946.

TABLE 1.—*The Synergistic Activity of Single Doses of Penicillin in Isotonic Solution of Sodium Chloride by Intramuscular Injection with a Single Dose of Oraphenarsine Hydrochloride by Intravenous Injection*

No.	Penicillin, Units per Kg.	Oraphenarsine Hydrochloride, Mg. per Kg.	Results of Dark Field Examination for T. Pallidum, Days *							Results of Transfer of Lymph Nodes
			1	2	3	7	14	21	28	
1.....	10,000	1.0	2	1	1	—	—	—	—	—
2.....	10,000	1.0	2	1	—	—	—	—	—	Negative
3.....	20,000	1.0	2	1	—	—	—	—	—	Negative
4.....	20,000	1.0	1	1	—	—	—	—	—	Negative
5.....	30,000	1.0	1	1	—	—	—	—	—	Negative
6.....	30,000	1.0	1	1	—	—	—	—	—	Negative
7.....	.....	1.0	4	2	1	—	4	1	4	Positive
8.....	.....	1.0	4	2	—	—	2	4	4	Positive

\* After institution of treatment: 4 indicates large numbers of actively motile spirochetes per dark field; 3, 2 and 1 indicate smaller numbers of spirochetes per dark field respectively; — indicates negative results on dark field examinations.

TABLE 2.—*The Synergistic Activity of Single Doses of Penicillin and Oraphenarsine Hydrochloride in Peanut Oil and Beevax by Intramuscular Injection*

No.	Penicillin, Units per Kg.	Oraphenarsine Hydrochloride, Mg. per Kg.	Results of Dark Field Examination for T. Pallidum, Days *							Results of Transfer of Lymph Nodes
			1	2	3	7	14	21	28	
1.....	2,000	2.0	2	1	—	—	—	—	—	Negative
2.....	2,000	2.0	1	1	—	—	—	—	—	Negative
3.....	5,000	2.0	1	1	—	—	—	—	—	Negative
4.....	5,000	2.0	1	1	—	—	—	—	—	Negative
5.....	10,000	2.0	1	—	—	—	—	—	—	Negative
6.....	10,000	2.0	1	—	—	—	—	—	—	Positive
7.....	.....	2.0	1	—	—	4	4	4	4	Positive
8.....	.....	2.0	1	1	—	2	4	4	4	Positive

\* After institution of treatment: 4 indicates large numbers of actively motile spirochetes per dark field; 3, 2 and 1 indicate smaller numbers of spirochetes per dark field respectively; — indicates negative results on dark field examinations.

## CLINICAL DIAGNOSIS

It is not possible to make a positive clinical diagnosis of histoplasmosis. It should be considered in infants and adults with various obscure symptoms. While anemia, enlargement of the liver, spleen and lymph nodes, leukopenia, emaciation and fever are usually observed, there may be considerable variation in the clinical observations. The disease may be of long or short duration and may mimic many other conditions.

The cutaneous and mucus membranous lesions of histoplasmosis may resemble closely the involvement seen in tuberculosis, syphilis and deep mycoses. The signs and symptoms observed in lymphoblastomas, especially Hodgkin's disease, leukemia and lymphosarcoma, may be simulated by histoplasmosis. It must be distinguished from kala-azar, malaria, dysentery, typhoid, paratyphoid and neoplasm. The impetiginized, furunculoid and crusted lesions seen in histoplasmosis must be differentiated from impetigo, ecthyma and pyoderma in general. Lack of knowledge of the disease is the main cause of failure in making a diagnosis.

## SYSTEMIC MANIFESTATIONS

The clinical picture of histoplasmosis is a variable one. The patients usually have a septic temperature, anemia and leukopenia. In many instances the lymph nodes are enlarged, suggesting Hodgkin's disease or one of the other lymphoblastomas. Pulmonary or adrenal involvement may be a prominent feature, and terminally active tuberculosis may be coexistent. Endocarditis, ulcerative enteritis and involvement of joints due to histoplasmosis have been reported. Occasionally a patient is observed with a localized lesion of recent development which may have resulted from a new infection or may represent renewed activity of a benign and quiescent form of the disease acquired in childhood. In most instances, the infection is progressive and disseminated in character. The systemic manifestations are described in detail by Meleny,<sup>31</sup> Parsons and Zarafonetis<sup>1</sup> and other authors and will not be discussed further in this paper.

Cutaneous or mucomembranous lesions are observed in many patients with this disease. The following résumé of such lesions in reported cases and the subsequent report of a case will stress the various cutaneous manifestations that have been noted.

OCCURRENCE OF CUTANEOUS AND MUCOMEMBRANOUS LESIONS  
IN REPORTED CASES

The types of cutaneous and mucomembranous lesions described in the literature may be classified in five groups:

sarcoids. In most instances the lesions, which were single or multiple, subsequently ulcerated, leaving punched-out, ovoid, slightly infiltrated ulcers covered with hemorrhagic crusts. In some patients with these punched-out ulcers of the skin the disease apparently was present from eight to sixteen years before the ulcers developed. In the more fulminating types of histoplasmosis the ulcers appeared earlier. Histologic examination of biopsy material obtained from the borders of the ulcers usually established the diagnosis.

3. *Purpuric Lesions*.—Purpuric lesions were reported in 7 patients.<sup>18</sup> In 3, purpuric areas measuring from a few millimeters to 4 cm. in diameter were observed within a few weeks to several months before death. Some of the lesions subsequently ulcerated. The yeastlike cells of *H. capsulatum* were observed in material removed from the ulcers.

In 5 cases petechial hemorrhages developed over the chest and abdomen two or three days before death. Most of the patients in this latter group were infants.

4. *Abscesses, Furunculoid and Impetiginized Areas*.—Strong's<sup>2a</sup> patient had a chronic abscess on the wall of the chest with no other signs or symptoms. One of the patients reported by McLeod and his associates<sup>2i</sup> had walnut-sized boils on the scalp. Organisms which in retrospect were believed to be *H. capsulatum* were demonstrated in material from the lesions of both patients.

An infant reported by Beamer and his associates<sup>3y</sup> had "... intact, ruptured or encrusted vesicles" 2 to 3 mm. in diameter all over the body from 4 days until 10½ months of age, at which time it died of histoplasmosis. The eruption was diagnosed as impetigo, with no record of cultural or histologic studies of the lesions. Rhodes and his associates<sup>3v</sup> also reported the presence of "impetigo" on the face of a 3 month old infant with histoplasmosis. Iams<sup>2q</sup> stated that in an infant 3 months of age with histoplasmosis "... a peculiar pustular rash appeared on the chest and back, for which a diagnosis of pyoderma was made." No search was made for the organisms in the cutaneous lesions of these patients.

5. *Dermatitis, Local or Generalized*.—Shaffer and his associates<sup>3k</sup> reported scaling of the skin of the hands and feet in an 11 month old infant with histoplasmosis. De Almeida and da Silva Lacaz<sup>3t</sup> observed *H. capsulatum* in areas of verrucous dermatitis, and Negroni<sup>3z</sup> recovered the organisms from a patient with vegetating and ulcerated lesions.

Hansmann and Schenken<sup>31</sup> observed a man 43 years of age who had an eruption for the last sixteen years of his life. It began in his

18. Schlumberger and Service.<sup>21</sup> Shaffer, Shaul and Mitchell.<sup>3k</sup> Gunter and Lafferty.<sup>3m</sup> Humphrey.<sup>3p</sup> Anderson, Michelson and Dunn.<sup>3r</sup> Thomas and Morehead.<sup>3x</sup> Hild.<sup>3n</sup>

TABLE 3.—Synergistic Activity of Multiple Doses of Penicillin in Isotonic Solution of Sodium Chloride by Intramuscular Injection and Multiple Doses of Oxophenarsine Hydrochloride by Intravenous Injection

No.	Penicillin *		Oxophenarsine Hydrochloride †		Results of Dark Field Examination for T. Pallidum, Days ‡								Results of Transfer of Lymph Nodes			
	Units per Kg.	Total	Mg. per Kg.	Total	1	2	3	7	14	21	28	35	42	49	56	63
1	550	4,000	0.2	1.6	2	1	—	—	—	—	—	—	—	—	—	Negative
2	250	4,000	0.2	1.6	2	1	—	—	—	—	—	—	—	—	—	Negative
3	500	8,000	0.2	1.6	1	—	—	—	—	—	—	—	—	—	—	Negative
4	500	8,000	0.2	1.6	1	—	—	—	—	—	—	—	—	—	—	Negative
5	1,000	16,000	0.2	1.6	1	—	—	—	—	—	—	—	—	—	—	Negative
6	1,000	16,000	0.2	1.6	1	—	—	—	—	—	—	—	—	—	—	Positive
7	....	....	0.2	1.6	4	4	—	—	—	—	—	—	—	—	—	Positive
8	....	....	0.2	1.6	4	4	—	—	—	—	—	—	—	—	—	Positive

\* Twice daily for eight days in succession.  
 † Once daily for eight days in succession.  
 ‡ After institution of treatment: 4 indicates large numbers of actively motile spirochetes per dark field; 3, 2 and 1 indicate smaller numbers of spirochetes per dark field respectively; — indicates negative results on dark field examinations.

TABLE 4.—Synergistic Activity of Multiple Doses of Penicillin in Peanut Oil and Beeswax by Intramuscular Injection and Multiple Doses of Oxophenarsine Hydrochloride by Intravenous Injection

No.	Penicillin *		Oxophenarsine Hydrochloride †		Results of Dark Field Examination for T. Pallidum, Days ‡								Results of Transfer of Lymph Nodes			
	Units per Kg.	Total	Mg. per Kg.	Total	1	2	3	7	14	21	28	35	42	49	56	63
1	1,000	8,000	0.2	1.6	2	1	—	—	—	—	—	—	—	—	—	Negative
2	1,000	8,000	0.2	1.6	1	—	—	—	—	—	—	—	—	—	—	Negative
3	5,000	40,000	0.2	1.6	1	1	—	—	—	—	—	—	—	—	—	Negative
4	5,000	40,000	0.2	1.6	1	1	—	—	—	—	—	—	—	—	—	Negative
5	10,000	80,000	0.2	1.6	1	1	—	—	—	—	—	—	—	—	—	Negative
6	10,000	80,000	0.2	1.6	—	—	—	—	—	—	—	—	—	—	—	Negative

\* Once daily for eight days in succession.  
 † Once daily for eight days in succession.  
 ‡ After institution of treatment: 4 indicates large numbers of actively motile spirochetes per dark field; 3, 2 and 1 indicate smaller numbers of spirochetes per dark field respectively; — indicates negative results on dark field examinations.

that the progression of each disease was enhanced by the debilitating effect of the other, and it is likelier that in most instances it was the histoplasmosis which activated the previously dormant old focus of tuberculosis.

The association of histoplasmosis with neoplasms involving the reticuloendothelial system has not been infrequent. Histoplasmosis associated with leukemia has been reported twice,<sup>20</sup> and with Hodgkin's disease once,<sup>1</sup> and this is the second report of its occurrence with Hodgkin's disease, but accompanied with a malignant lymphoma. In case 47 of Parsons and Zarafonetis<sup>1</sup> a diagnosis of lymphosarcoma in a lymph node was made by biopsy, but after a complete autopsy at a later date, these authors discovered no evidence of lymphosarcoma and concluded that the original biopsy slide may have been from a different patient. Besides the interesting phenomenon of the simultaneous association of histoplasmosis with the malignant lymphoma, there is the added problem of confusing the histoplasmosis tissue reaction with that of the malignant lymphomas. No doubt, an occasional cell is encountered in histoplasmosis which, by itself, is indistinguishable from the Sternberg-Reed cell type. It is also evident that fibrosis and chronic inflammatory cells, particularly plasma cells and lymphocytes, are abundant in each disease. While focal areas of accumulations of polymorphonuclear cells and even necrosis will occasionally occur in Hodgkin's disease, they are not usually seen. Histoplasmosis would be more prone to present such pseudotuberculous structures. With such features in common, there is no doubt that histoplasmosis might be confused with atypical Hodgkin's disease. However, it should be distinguished from the classic pattern of actively neoplastic Hodgkin's disease and especially from so-called Hodgkin's sarcoma. In the presence of known histoplasmosis, rigid criteria must be maintained before a diagnosis of coincident Hodgkin's disease can be accepted. If the subsequent clinical picture and observations at autopsy support the diagnosis of a neoplastic disease and particularly if Hodgkin's disease assumes some of its more sarcomatous manifestations, the coexistence of the two diseases may be accepted.

#### PATHOLOGY

Reactions of tissue, both gross and microscopic, to the presence of *H. capsulatum* have been described and carefully studied by several authors. Histoplasmosis belongs to the general group of chronic infectious granulomas, and it possesses no specific cytologic characteristics which separate it from the other members of his group. The basic cell reacting to the presence of the fungus is the macrophage, and the

20. Riehl.<sup>33</sup> Williams and Cromartie.<sup>34</sup>

TABLE 5.—*The Synergistic Activity of Single Doses of Penicillin in Peanut Oil and Beestear and of Bismuth and Potassium Tartrate in Oil by Intramuscular Injection*

No.	Penicillin, Units per KG.	Bismuth and Potassium Tartrate, Mg. per KG.	Results of Dark Field Examination for T. Pallidum, Days *									Results of Transfer of Lymph Nodes	
			1	2	3	7	14	21	28	35	42	49	
1.....	2,000	0.002	1	1	—	—	—	—	—	—	—	—	Negative
2.....	2,000	0.002	2	1	—	—	—	—	—	—	—	—	Negative
3.....	6,000	0.002	1	1	—	—	—	—	—	—	—	—	Negative
4.....	5,000	0.002	1	1	—	—	—	—	—	—	—	—	Negative
5.....	10,000	0.002	1	—	—	—	—	—	—	—	—	—	Negative
6.....	10,000	0.002	1	—	—	—	—	—	—	—	—	—	Negative
7.....	.....	0.002	2	1	—	2	4	4	4	4	4	4	Positive
8.....	.....	0.002	2	1	—	4	4	4	4	4	4	4	Positive

No.	Penicillin *	Bismuth and Potassium Tartrate †	Results of Dark Field Examination for T. Pallidum, Days ‡									Results of Transfer of Lymph Nodes					
			Total	Gm. per Kg.	1	2	3	7	14	21	28	35	42	49	56	63	70
1	1,000	8,000	0.0005	0.002	2	1	—	—	—	—	—	—	—	—	—	—	Negative
2	1,000	8,000	0.0005	0.002	1	1	—	—	—	—	—	—	—	—	—	—	Negative
3	2,000	16,000	0.0005	0.002	1	—	—	—	—	—	—	—	—	—	—	—	Negative
4	2,000	16,000	0.0005	0.002	1	—	—	—	—	—	—	—	—	—	—	—	Negative
5	5,000	40,000	0.0005	0.002	1	—	—	—	—	—	—	—	—	—	—	—	Negative
6	5,000	40,000	0.0005	0.002	1	—	—	—	—	—	—	—	—	—	—	—	Negative
7	.....	.....	0.0005	0.002	4	4	4	4	2	—	—	4	4	4	4	4	Positive
8	.....	.....	0.0005	0.002	4	4	4	4	4	2	—	—	—	—	—	—	Positive

\* Once daily for eight days in succession.  
† Four doses, given on the second, fourth, sixth and eighth days of treatment.  
‡ After institution of treatment: 4 indicates large numbers of actively motile spirochetes per dark field; 3, 2 and 1 indicate smaller numbers of spirochetes per dark field respectively; — indicates negative results on dark field examinations.

182 TABLE 6.—*Synergistic Activity of Multiple Doses of Penicillin in Isotonic Solution of Sodium Chloride and of Bismuth and Potassium Tartrate in Oil by Intramuscular Injection*

No.	Penicillin *	Bismuth and Potassium Tartrate †	Results of Dark Field Examination for T. Pallidum, Days ‡									Results of Transfer of Lymph Nodes					
			Total	Gm. per Kg.	1	2	3	7	14	21	28	35	42	49	56	63	70
1	1,000	8,000	0.0005	0.002	2	1	—	—	—	—	—	—	—	—	—	—	Negative
2	1,000	8,000	0.0005	0.002	1	1	—	—	—	—	—	—	—	—	—	—	Negative
3	2,000	16,000	0.0005	0.002	1	—	—	—	—	—	—	—	—	—	—	—	Negative
4	2,000	16,000	0.0005	0.002	1	—	—	—	—	—	—	—	—	—	—	—	Negative
5	5,000	40,000	0.0005	0.002	1	—	—	—	—	—	—	—	—	—	—	—	Negative
6	5,000	40,000	0.0005	0.002	1	—	—	—	—	—	—	—	—	—	—	—	Negative
7	.....	.....	0.0005	0.002	4	4	4	4	2	—	—	4	4	4	4	4	Positive
8	.....	.....	0.0005	0.002	4	4	4	4	4	2	—	—	—	—	—	—	Positive

\* Once daily for eight days in succession.  
† Four doses, given on the second, fourth, sixth and eighth days of treatment.  
‡ After institution of treatment: 4 indicates large numbers of actively motile spirochetes per dark field; 3, 2 and 1 indicate smaller numbers of spirochetes per dark field respectively; — indicates negative results on dark field examinations.

During the following month, there was a gradual increase in the size of the ulcer and microscopic examination of the necrotic tissue indicated that numerous organisms were still present. From March 17 to 29, during a course of roentgen therapy, a total of 1,000 r was given to the left half of the ulcer. No appreciable effect was noted. The generalized lymphadenopathy had not changed. The spleen was not palpable, and the liver was felt 4 cm. below the xiphoid process. Tests of hepatic function showed some impairment.

From April 8 to 14, a total of 4.2 Gm. of "neostam" was given intravenously. Daily oral doses of 6 Gm. of para-aminobenzoic acid were administered concurrently to prevent hepatic damage. Loss of weight, mild anemia and leukopenia (4,200 leukocytes) were noted during this period. However, on May 5 the results of the tests of hepatic function were normal. There was no change in the ulcer of the tongue. The usual intermittent fever continued and was augmented by febrile responses up to 40 C. (104 F.) as a result of the injections of "neostam" given every other day.

On May 11, sternal marrow and blood cultures were again negative. Reactions in intradermal tests employing an antigen prepared with the fungus isolated from the patient were negative, although a complement fixation test utilizing the same antigen elicited a positive reaction.

On May 19, penicillin was given by the intravenous drip method, despite the fact that laboratory tests demonstrated that the fungus isolated from the patient was not sensitive to it. A total of 1,300,000 units was given in eleven days. The intermittent fever was unchanged. The tongue was becoming painful, and the ulcer increased in size. This was still the only evident lesion from which the organism could be readily demonstrated in direct smears, in biopsy and by culture. The liver had increased in size, reaching the umbilicus. The spleen was not palpable. Loss of weight was slow but progressive, influenced perhaps by the difficulty in eating, although a stomach tube was used because of pain in the tongue. Terminal bronchopneumonia developed, followed quickly by coma and death on June 8, 1944.

*Biopsy of Cervical Lymph Node* (removed elsewhere February 1938, but first examined by us in December 1943).—The general outline of the lymph node was well preserved. However, examination for detail of pattern showed an obliteration of the sinusoids in the lymph node by an increased number of cells of the lymphocytic type. Some round cell reaction was noted, particularly of the plasma cell type, but no eosinophils were encountered. Fibrosis was not prominent, and the capsule of the lymph node was not invaded. Macrophage reaction was not evident, and no formation of tubercles, necrosis or Langhans type of giant cell was seen. Scattered throughout the node were large cells of reticuloendothelial type having multiple nuclei, which in some instances were lobulated and which not infrequently had a prominent central nucleolus. These cells had a somewhat darkened, usually eosinophilic cytoplasm, and extensive pleomorphism within these cells was observed. At the time of the initial study *H. capsulatum* was not seen in any of the cells. However, exhaustive search at a much later date did reveal one small relatively normal-appearing macrophage that contained three structures microscopically characteristic of the fungus. The diagnosis was a cervical lymph node with cellular reaction microscopically characteristic of Hodgkin's paragranuloma and containing *H. capsulatum*.

*Biopsy of Tongue* (December 1943).—The superficial epithelium was ulcerated, revealing underlying chronically inflamed connective tissue, showing masses of round cells and some proliferation of connective tissue. Scattered throughout

in oil was administered intramuscularly on the second, fourth, sixth and eighth days of treatment in doses of 0.0005 Gm. per kilogram, totaling 0.002 Gm.

#### SUMMARY

1. The intravenous injection of 1.0 mg. of oxophenarsine hydrochloride per kilogram (one-eighth to one-tenth of the single minimal curative dose) reduced the single minimal curative dose of penicillin by intramuscular injection from more than 100,000 units to probably less than 10,000 units per kilogram in the treatment of acute syphilitic orchitis of rabbits.
2. The intramuscular injection of 2.0 mg. of oxophenarsine hydrochloride per kilogram in peanut oil and beeswax reduced the single minimal curative dose of penicillin in peanut oil and beeswax from approximately 10,000 units to 2,000 units or less per kilogram.
3. The intravenous injection of 0.2 mg. of oxophenarsine hydrochloride per kilogram once a day for eight days in succession (1.6 mg.) reduced the minimal curative dose of approximately 1,000 units of penicillin per kilogram twice daily for eight days in succession by intramuscular injection (totaling 16,000 units) to 250 units or less per kilogram (totaling 4,000 units or less).
4. The intravenous injection of 0.2 mg. of oxophenarsine hydrochloride per kilogram once a day for eight days in succession (1.6 mg.) reduced the minimal curative dose of approximately 5,000 units of penicillin per kilogram once daily for eight days in succession (totaling 40,000 units) to 1,000 units or less per kilogram (totaling 8,000 units or less).
5. The intramuscular injection of 0.002 Gm. of bismuth and potassium tartrate in peanut oil and beeswax per kilogram of weight (one-fifth the single minimal curative dose) reduced the single minimal curative dose of penicillin in peanut oil and beeswax from approximately 10,000 units to probably less than 2,000 units per kilogram.
6. The intramuscular injection of 0.0005 Gm. of bismuth and potassium tartrate in peanut oil and beeswax per kilogram on the second, fourth, sixth and eighth days of treatment (totaling 0.002 Gm.) reduced the minimal curative dose of penicillin in isotonic solution of sodium chloride administered intramuscularly once a day for eight days in succession from approximately 5,000 units (totaling 40,000 units) to 1,000 units or less (totaling 8,000 units or less) per kilogram of weight.
7. Under the conditions, not only oxophenarsine hydrochloride by intravenous and intramuscular injection but bismuth and potassium tartrate in oil by intramuscular injection has shown decided synergistic or additive therapeutic effects in the treatment of acute syphilitic orchitis of rabbits with penicillin.

scattered macrophages morphologically characteristic histoplasma organisms were noted. These macrophages contained only one to three organisms and never large masses of them. An occasional macrophage was multinucleated and did not have a prominent nucleolus, so that it was morphologically identical with the so-called Sternberg-Reed cell seen in Hodgkin's disease. However, the definite chronic granulomatous pattern of this portion of the lymph node with the distinct predominance of the macrophage type of cell lent an over-all microscopic picture which in no way suggested the presence of Hodgkin's disease. The diagnosis was a lymph node containing an old focus of tuberculosis and a granulomatous reaction revealing *H. capsulatum*.



Fig. 3.—*Histoplasma capsulatum* in a section of the tongue.  $\times 1,000$ .

*Report of Autopsy.*—Only pertinent observations of the autopsy performed in June 1944 will be discussed.

Examination of the body revealed advanced wasting of all the tissues. The mouth was normal except for the tongue, on which was seen an indurated ulcer 0.5 cm. deep and 3 cm. in diameter. The lymph nodes were not significantly enlarged. The heart was within normal limits in size and structure. Each pleural cavity contained about 1,000 cc. of straw-colored clear fluid and was free of adhesions. Both lungs were moderately congested and showed bilateral apical scarring, characteristic of old tuberculous foci. In addition, there were necrotic-appearing nodules 2 to 3 mm. in diameter, resembling small tubercles, which were scattered widely throughout the lungs. The hilar lymph nodes were small, but grossly caseous. The liver weighed 2,300 Gm. and was studded throughout by multiple

## PYODERMA GANGRENOsum IN ULCERATIVE COLITIS

Report of a Case

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ULCERONECROTIC lesions of the skin occurring in association with chronic ulcerative colitis have previously been described by Felsen,<sup>1</sup> Greenbaum,<sup>2</sup> Jones,<sup>3</sup> Brunsting<sup>4</sup> and Cohen<sup>5</sup> under the terms pyoderma gangrenosum and ecthyma gangrenosum. The following case is reported because such lesions are rare and their causation is still controversial.

Felsen described 3 cases in 1941 and reported *Escherichia coli*, *Staphylococcus aureus* and nonhemolytic streptococcus in his cases 1, 2 and 3, respectively. He concluded, therefore, that a single bacterial agent is not responsible and expressed the belief that the lesions were probably due to a nutritional disturbance. In reporting 6 cases, Greenbaum also commented on the divergent bacteria observed. His attempts to reproduce lesions by inoculation with a single viable organism failed but were successful when pus was injected into patients in 2 cases and when two organisms were injected simultaneously into patients in 4 cases. He questioned the possibility of a nonbacterial (allergic) factor's being a necessary complement to development of the disease. Jones stated the belief that the lesions were due to deficiency in diet and colonic infection. Cohen reported 1 case in 1936 and pointed out that such lesions are part of a syndrome including recurrence of colitis, hypochromic anemia, hypoproteinemia, fever and foci of infection elsewhere in the body. He considered the cause to be nutritional disturbance with lowered resistance of the skin and secondary bacterial invasion but mentioned elimination of infected teeth as important in curing his patient.

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From Lawrence Hospital.

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2. Greenbaum, S.: Inoculation Studies with Viable Bacteria Cultured from Lesions of Pyoderma Gangraenosum, Arch. Dermat. & Syph. **43**:775 (May) 1941.
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4. Brunsting, L. A.; Goeckerman, W. H., and O'Leary, P. A.: Pyoderma (Ecthyma) Gangrenosum, Arch. Dermat. & Syph. **22**:655 (Oct.) 1930.
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*Laboratory Diagnosis.*—Direct examination of material removed from suspected lesions may result in an immediate diagnosis of histoplasmosis. With our patient the characteristic yeastlike cells readily could be seen in stained preparations of material scraped from the periphery of the lesion of the tongue. In such preparations the organism is seen in large mononuclear or epithelial cells and appears as a small oval body, 1 to 4 microns in length and surrounded by a nonstaining capsule. The deeply staining chromatin material of the cell is concentrated in a crescent-shaped mass at one pole of the organism, giving a signet ring appearance to the parasite. In dried stained impression smears of biopsy material and in sections of tissue the fungus may be confused with the leishmania stage of Leishmania donovani, Leishmania tropica or Leishmania braziliensis, the protozoan parasites causing visceral, cutaneous and American leishmaniasis, respectively. The presence of a rod-shaped kinetoplast and absence of a capsule are characteristics of the Leishmaniae which serve to differentiate these organisms from the yeastlike cells of *H. capsulatum*.

Although a provisional diagnosis may be established on the basis of finding the organisms in thick or thin smears of peripheral blood, in smears of sternal bone marrow, in smears or sections of biopsy specimens or in splenic pulp obtained by puncture, every effort should be made to confirm the observations by isolation of the fungus in cultures. *H. capsulatum* will develop in a variety of laboratory mediums. Sheep blood agar, Sabouraud's dextrose agar, Peppler's<sup>23</sup> buffered medium and beef heart hormone broth and agar containing cystine monohydrochloride and sodium sulfite were the mediums most frequently employed for the isolation of the fungus from specimens obtained from our patient as well as for the preparation of antigens for serologic and intradermal tests. In most instances plates, flasks or slants were inoculated in pairs, one of the cultures incubated at 37 C. and the other kept at room temperature. Primary isolation of the fungus from tissue fragments and biopsies was most effectively obtained on sheep blood agar plates kept at room temperature. On this medium young colonies of *H. capsulatum* are small, slightly raised, rough, dull appearing and dark brown and have an irregular edge. A period of growth of five to seven days is required before the colonies acquire an appreciable size and develop differential characteristics. Microscopically the young colonies show branching septate hyphae on which are borne small (3 to 6 microns in diameter) spherical or pyriform spores with smooth walls. These arise directly on the walls of the hypha or on short stalks. With continued growth the colony develops a typical fungous appearance with the production of a white cottony aerial mycelium in from nine to fourteen days. Microscopically this older colony shows spherical, oval or pyriform smooth-walled spores, varying considerably in size (5 to 18 microns in diameter), and large (18 to 25 microns in diameter) tuberculate, spherical or pyriform spores, containing one or several usually round fat globules. The protuberances of these tuberculate spores may reach 6 to 8 microns in length. Both of these spore types may be sessile or pedicellate. The mycologic diagnosis of histoplasmosis is based primarily on the presence in cultures of the large tuberculate spores. This characteristic morphologic feature of *H. capsulatum* serves to differentiate this fungus from others possessing similar mycelia and spores.

The yeast phase of the fungus was obtained in culture by inoculating blood slants with young colonies picked from blood plates kept at room temperature. The slants were sealed with "parafilm" and incubated at 37 C. Serial transfers

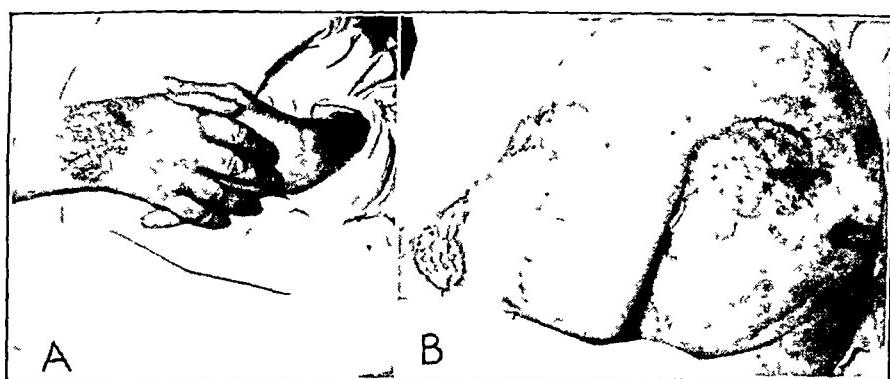
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## REPORT OF A CASE

*History.*—Mrs. F., a white woman aged 38, was admitted to Lawrence Hospital on Sept. 26, 1944 with the chief complaints of fever, stiffness of the right side of the neck, painful swelling of the right wrist and mild colitis. The present illness began acutely three days before admission.

Her past history revealed that eight years previously she had had "arthritis" in the right wrist and that since then the wrist had been stiff. Three years previously she had been seriously ill and had been hospitalized for several months with ulcerative colitis, diagnosis of which was confirmed by roentgenograms and biopsy. Stool cultures yielded *Esch. coli*, *Escherichia coli hemolytica* and some strings of streptococci. No ova or amebas were observed. The patient was told that colitis was secondary to infection of the teeth, but she neglected to have treatment for this condition. Since then she had been fairly well except for mild colitis.

On admission the patient was well nourished and weighed 156 pounds (70.8 Kg.). Her temperature was 102 F., and she was acutely ill. There was gross



*A*, lesion of the wrist during the fifth week of illness; *B*, lesions of the buttocks during the tenth week of illness.

evidence of infected teeth. The right wrist was red, swollen and stiff. Examination disclosed no other significant abnormalities. The skin was clear on admission, but a few days later a small impetiginous pustule was noted on the right buttock. This later proved to be the first of a series of cutaneous lesions which soon dominated the clinical picture. The pustule opened spontaneously and drained a thin purulent exudate. The lesion continued to enlarge into a rapidly growing ulcer, which at the end of two months was 5 inches (12.7 cm) in diameter. At the beginning of her third week of hospitalization two small ulcerative lesions developed on the right wrist, and within a week these coalesced to form an ulcer 2 inches (5 cm.) in diameter. During the following week similar lesions developed on the left buttock, both thighs and the entire under surface of both breasts. During the fifth week an erythematous nodule appeared on the right leg. During the next few days this had become a large vesicular lesion 2 inches in diameter. This soon developed into a rapidly growing ulcer, which by the eighth week of hospitalization completely circled the leg from knee to ankle. During these first two months the patient's general condition had become more critical. Temperature of 102 F. had persisted, and the colitis was severe. The patient lost a great deal of weight and was pale.

Histoplasmosis has been observed to be coexistent with tuberculosis, leukemia and Hodgkin's disease. While histoplasmosis may simulate Hodgkin's disease microscopically, our patient had coexistent Hodgkin's disease, as indicated by the clinical course of the disease and by the discovery at autopsy of a malignant lymphoma, best classified as so-called Hodgkin's sarcoma.

A diagnosis of histoplasmosis cannot be made on clinical signs alone. Biopsy of skin or of lymph nodes is the most successful method of diagnosis during life. Examination of blood smears, bone marrow and splenic pulp obtained by puncture may be of value, but in all instances the diagnosis must be confirmed by isolation of the fungus in culture. Intradermal and complement fixation tests may be helpful. In our patient the histoplasmin, coccidioidin and haplosporangin tests gave equivocal results. The reaction to Napier's serum test was negative and to Wolff's precipitation test positive.

The sources of infection, the modes of transmission and the portals of entry of *H. capsulatum* are not known. Animal to man or man to man transmission may occur. Pulmonary calcification may be due to a benign infection with *H. capsulatum*, but cross reactions with histoplasmin, blastomycin, coccidioidin and haplosporangin prevent such an assumption now.

There is no satisfactory treatment for a disseminated infection with *H. capsulatum*. Arrest of some localized lesions has been reported with various remedies. "Neostam," sulfadiazine, penicillin and roentgen ray therapy were unsuccessful in our patient.

384 Post Street.

#### ABSTRACT OF DISCUSSION

DR. JAMES H. MITCHELL, Chicago: I should like to report a case which has not been published and which should be added to the number already reported by Dr. Miller. The patient, a woman, was seen two years ago. She had spent the winter in Florida. She returned to Chicago in failing health and was a patient of Dr. William Thomas of the Presbyterian Hospital. He referred her to Dr. Vernon David for operation on the gallbladder. Dr. David, however, refused to operate because of her condition, which was poor. She had all the signs and symptoms, such as anemia, leukopenia, enlarged spleen and oscillating temperature, and had lost a great deal of weight.

I was asked to see her because she had a generalized papular eruption. These papules were suggestive of tuberculids of the ulcerated type.

She had a productive cough, and the roentgenograms of the lungs indicated a great deal of activity of one kind or another, but no diagnosis was made by the roentgenologist.

The patient was so ill that I hesitated to do a biopsy, but, nevertheless, this was done. There was a symmetric generalized distribution of papules with a lesion in the left labial commissure similar to the lesion described by Palmer, Amolsch and Shaffer.<sup>37</sup> The preliminary diagnosis given by the pathologist before I saw the section was "nonspecific inflammatory reaction," but before I

*Description of Lesions.*—The lesions began as slightly raised erythematous nodules resembling erythema nodosum. The nodules were several centimeters in diameter. A vesicle filled with cloudy gray or hemorrhagic fluid or a soft area soon developed in the center of each nodule. This sloughed out in a few days, the epidermis remaining for a time as a thin gray translucent film over the crater. The resulting ulcer was phagedenic and grew rapidly. The edge of the ulcer seemed to melt away, so rapidly did the sloughing occur. The base consisted of a soft, boggy, pale and unhealthy-looking granulation tissue covered with thin grayish yellow mucopurulent exudate. The edges of the ulcer were raised and slightly undermined. The dead skin along the edge could be peeled off, and the skin under it had a pearly gray appearance. The skin surrounding the ulcer was indurated and red for about  $\frac{1}{2}$  inch (1.27 cm.), and there were small satellite vesicles in this area. The ulcers were irregular in shape, roughly circular and varied in size. The distribution was roughly symmetric. The lesions did not spread to contiguous surfaces, as evidenced by the lesions on the breasts where inability to keep dressings in place meant that the ulcer touched the adjacent thoracic wall without inducing lesions. The lesions were tender. Healing, which coincided with improvement in the patient's general condition, was characterized by epithelization from the edges of the ulcer and from islands of epithelium which appeared in the center of the lesions. Large scars resulted.

*Laboratory Data.*—The blood count on admission showed 95 per cent hemoglobin and 5,900 white blood cells with 77 per cent polymorphonuclear leukocytes, 92 per cent of which were young forms. A month later the hemoglobin was 65 per cent and the leukocyte count was 10,700 with 46 per cent polymorphonuclear leukocytes, 82 per cent of which were young forms. The urine showed a trace of albumin and many pus cells. The first cultures of the cutaneous lesions showed only a diphtheroid. Cultures of a freshly opened vesicle, which were made to rule out secondary contamination by cutaneous organisms, were negative both aerobically and anaerobically. Cultures for blastomycosis, actinomycosis and sporotrichosis were negative. A smear from a vesicle showed many polymorphonuclear leukocytes and red cells but no organisms or amebas. A biopsy of the margin of one of the ulcers showed a simple ulcerative process in the skin extending down into the fat. The reaction was almost wholly polymorphonuclear in type. The margins of the skin showed the remnants of blebs with loose epithelial cells in the fluid beneath the epidermis. There was no evidence of distinctive granuloma about the ulcer. The subcutaneous tissues near the ulcer were essentially normal. The Wassermann reaction of the blood was negative, and blood cultures were negative both aerobically and anaerobically. A roentgenogram of the teeth showed many root fragments with apical abscesses. A roentgenogram of the chest showed a few fibrotic strands and calcified nodes, suggesting an old infection with tuberculosis. A roentgenogram of the right wrist showed decided increased density of the lateral half of the semilunar bone. The stools were described as mucopurulent and bloody. Stool cultures showed *Streptococcus viridans*. No amebas or ova were observed.\*

*Treatment and Course.*—The patient was treated with vitamins, liver and iron and whole blood transfusions. Penicillin, 20,000 units intramuscularly every three hours, was given for ten days at the end of the first month. There was no improvement in the lesions present, but after this no new ones developed. Fever and colitis continued, and her general condition was critical. All lesions continued to spread at an alarming rate. During the seventh week penicillin therapy was started again, and three abscessed teeth were extracted. Cultures

This patient was treated with sulfadiazine, penicillin and various other drugs prior to the opportunity which my associates and I had to make intensive studies. This led us to pursue various investigations with perhaps more avidity and thoroughness than usual. Everything which we tested gave negative results. I should like to ask Dr. Miller to say when he closes whether in this case he followed the patient after considerable treatment with the idea that the organisms were destroyed in the available tissues, and I should also like to ask whether the leukopenia was constant throughout.

The diagnosis of histoplasmosis is not always easily made, in spite of the reproductions that Dr. Miller and Dr. Mitchell have shown. I think that both of the discussers deserve credit for arriving at a definite diagnosis prior to death. We know that most of the published cases are found at autopsy.

We should be on the lookout for these cases, which are undoubtedly more numerous than the published number would lead us to believe.

DR. FREDERICK R. SCHMIDT, Chicago: I was interested in Dr. Miller's presentation because of my experience with the differential diagnosis of these tumors. About two years ago, in conjunction with a pathologist, Dr. Tuda, I reported 3 cases of so-called myoblastoma, in which we observed a nodule on the tongue, with ulcers on the skin similar to those in the pictures shown by Dr. Miller.

When we first saw the sections, we thought that the large vacuolated cells were those of histoplasmosis, but after eliminating that possibility, we did not know what they were until we saw an article by Klemperer in which were pictures of an abnormality similar to that in our patients. I do think, especially in the differential diagnosis of nodules of the tongue, that we should also consider so-called myoblastomas.

DR. HIRAM E. MILLER, San Francisco: I wish to thank the men who have discussed this presentation, especially Dr. Mitchell for giving some of the cultural characteristics of the organism which time prevented me from giving.

In answering Dr. Lewis, the presence of organisms was substantiated by smears, cultures or biopsy after each type of treatment and at other regular intervals. They continued to be observed in increasing numbers throughout the course of the disease.

Blood counts were essentially normal when the patient was first observed, but leukopenia developed when he began to lose weight, and it persisted until his death.

As Dr. Montgomery has brought out (Dr. Montgomery requested that his discussion of this paper be omitted from the record), there are several organisms that are closely related to Histoplasmosis capsulatum, and these have been reported by many observers. This is especially true in animals. Organisms resembling *H. capsulatum* have been observed in the dog, in the mouse and in a ferret, but only in the dog has it been specifically identified by its cultural characteristics. The dog, as a domestic pet, could serve as a reservoir for the infection. The report by McLeod of 2 cases of histoplasmosis in brothers who slept together may be an example of man to man transmission of the disease.

I feel reasonably certain that I have made a diagnosis of lymphoblastoma in patients with generalized cutaneous eruptions who may possibly have had histoplasmosis. In the final analysis, lack of knowledge of the disease is the main reason for not making a correct diagnosis.

of the teeth showed *Str. viridans* and *Staphylococcus albus*. During the eighth week the lesion on the wrist which had been dressed with plain petrolatum gauze showed evidence of healing, but all other lesions which had been similarly dressed were much worse. Zinc peroxide paste was tried on the lesions without success. At the end of the eighth week wet dressings of tyrothricin were applied for one-half hour followed by continuous dressings of petrolatum gauze. This subsequently proved to be the best method for keeping the lesions clean and the patient comfortable.

The ninth week the patient showed the first indications of improvement. The temperature fell to 100 F. "Kaopectate" (kaolin and pectin) helped to control the diarrhea, and treatment with "sulfasuxidine" begun at the end of this week seemed to clear the pus and blood in the stools. Plasma transfusions were given because the patient had edema of the face and low serum protein with inversion of the albumin-globulin ratio. Cultures of lesions at this time yielded *Proteus* organisms, *Bacillus pyocyanus*, *Esch. coli*, *Staphylococcus aureus* and *Str. viridans*. During the tenth week, two more teeth were extracted, cultures of which yielded *Streptococcus hemolyticus*, *Staph. aureus* and *Str. viridans*. Cutaneous tests were performed using vaccines made from these cultures. Vaccines of the first two organisms gave a reaction of immunity, but during the next two weeks, two small vesicular lesions similar to the beginnings of the large cutaneous lesions slowly developed at the two sites of the tests made with the *Streptococcus viridans* vaccine. These ultimately healed, leaving small scars. Two more teeth were extracted during the eleventh week. The following week the patient showed definite improvement. The temperature was normal, and the colitis was improved. The lesions of the breasts were healed, and new skin was present in the center and around the edges of all cutaneous lesions. The blood count was improved, showing hemoglobin 70 per cent, white blood cells 9,800 with 72 per cent polymorphonuclear neutrophils, 22 per cent of which were young forms. Improvement continued during the fourth month of hospitalization. Various ointments were tried to hasten healing, but petrolatum gauze seemed most soothing to the patient. When discharged the patient weighed 116 pounds (52.6 Kg.), a loss of 40 pounds (18.1 Kg.) since admission. Since discharge she has been well and has regained normal weight.

#### SUMMARY

A case of necrotic ulceration of the skin associated with recurrence of ulcerative colitis, bone marrow depression, hypoproteinemia and fever is described. Healing of the cutaneous lesions coincided with the general improvement which seemed to follow removal of focal dental infection. Cutaneous tests with vaccine made from *Streptococcus viridans* cultured from the teeth caused small vesicular lesions which resembled the first stage of large cutaneous lesions.

#### CONCLUSION

Ulceronecrotic lesions of the skin (*pyoderma gangrenosum*), and possibly the ulcerative colitis with which such lesions are associated, may be manifestations of an allergic reaction to bacterial infection elsewhere in the body, in this case dental abscesses.

These authors expressed the belief that this is a symptom rather than a clinical entity. According to Montgomery and Sullivan, Oppenheim did not regard the poikiloderma vasculare atrophicans of Jacobi as a real clinical or histopathologic entity, but stated the belief that some cases should be classified as acrodermatitis chronica atrophicans, others as poikilodermatomyositis and still others as secondary to various dermatoses. They concurred with this view. McCarthy<sup>7</sup> presented a detailed histologic description of poikiloderma. Weidman<sup>8</sup> used the pathologic diagnosis of poikiloderma vasculare atrophicans in classifying the material studied by him at the Laboratory of Dermatologic Research of the University of Pennsylvania.

Various types of this disease, including both localized forms and the generalized form, have been presented in the literature. Among the former, two types of pigmented dermatoses have been described—Riehl's melanosis and Civatte's *poikilodermie réticulée pigmentaire du visage et du cou*.

Hollander<sup>9</sup> stated that the term "Riehl's melanosis" should be reserved for the cases that were observed at the end of World War I and were first described by G. Riehl of Vienna. Riehl<sup>10</sup> reported cutaneous discolorations of bronze to chocolate color, localized on the face, especially the forehead, zygomatic region and temples, and spreading to the neck, ears (anterior and posterior auricular region) and scalp. The extensor surfaces of the forearms and hands and the axillary, mammary, umbilical and inguinal regions were rarely affected. The pigmentation started with discrete spots of various sizes, which later developed into diffuse melanotic areas. There were frequently white depigmented spots between the dark maculas. Numerous perifollicular macular or papular lesions, first reddish brown and later dark brown, could sometimes be seen. The skin was rough and somewhat scaly and looked as though it were covered with flour dust. Furthermore, numerous dilated follicular orifices, obstructed by keratotic material, could be seen on the forehead, cheeks and ears. No inflammatory signs, either exudation or atrophy, were reported. No subjective complaints were registered. Riehl thought that his melanosis was caused by toxic substances ingested with food, probably flour from different plant seeds—*Vicia fava* for instance, containing Bloch's pigment precursor, dopa, which was used in the production of bread during the war.

7. McCarthy, L.: Histopathology of Skin Diseases, St. Louis, C. V. Mosby Company, 1931, pp. 78-80.

8. Weidman, F.: Histologic Protocols, personal communication to the authors (1945).

9. Hollander, A.: Personal communication to the authors.

10. Riehl: Ueber eine eigenartige Melanose, Wien. klin. Wchnschr. 25:780, 1917.

## REITER'S DISEASE

A Comparison with Keratosis Blennorrhagica and with Psoriasis Arthropathica

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ALTHOUGH Reiter<sup>1</sup> originally described the syndrome bearing his name in 1916, the first case in the English literature was not reported until 1928.<sup>2</sup> However, the disease was not fully accepted in this country until after the report of Bauer and Engelman in 1942.<sup>3</sup> Since 1944 an increasing number of papers on this subject have been presented in the domestic literature. In view of the increasing interest in this disease, a comparison with keratosis blennorrhagica and with psoriasis arthropathica is indicated.

Observations in 75 cases of keratosis blennorrhagica and in 33 cases of psoriasis arthropathica were compared in 1939.<sup>4</sup> This study failed to demonstrate more than a superficial resemblance between the two diseases. Despite the overwhelming evidence that keratosis blennorrhagica and psoriasis arthropathica are distinct entities admitting accurate differentiation, the conviction persisted that some cases of keratosis were not caused by infection with gonococci. As evidenced by the correspondence received after the publication of the aforementioned article,<sup>4</sup> this belief was maintained by many dermatologists. The term "banal keratosis" seemed adequate for instances of keratosis-blennorrhagica-like eruptions not due to gonorrhreal infection. However, the increasing recognition of Reiter's disease as an entity forced its consideration in diagnosis of cases falling into this group. Briefly, Reiter's disease consists of urethritis, conjunctivitis and arthritis of unknown cause. Occasionally, cutaneous lesions occur, but in most instances there are no dermatologic manifestations. The more important eruptions have been described as balanitis circinata and, less frequently, as keratosis-blennorrhagica-like.

1. Reiter, H.: Ueber eine bisher unerkannte Spirochäteninfektion (Spirochaetosis arthritica), Deutsche med. Wochenschr. **42**:1535, 1916.

2. Frühwald, R.: So-Called Spirochaetosis Arthritis (Reiter, 1916), Urol. & Cutan. Rev. **32**:7 (Jan.) 1928.

3. Bauer, W., and Engelman, E. P.: A Syndrome of Unknown Etiology Characterized by Urethritis, Conjunctivitis and Arthritis (So-Called Reiter's Disease), Tr. A. Am. Physicians **57**: 307, 1942.

4. Epstein, E.: Differential Diagnosis of Keratosis Blennorrhagica and Psoriasis Arthropathica, Arch. Dermat. & Syph. **40**:547 (Oct.) 1939.

Oulmann,<sup>12</sup> and exposure to oily substances containing iron and arsenic. Hazen<sup>13</sup> mentioned a worker in tar. Many of the occupations listed in the literature are those in which there was exposure to physical factors, such as cold and sunlight, as is the case with coachmen, farmers and soldiers and also housewives and cooks, who may dip their hands in cold water.

*Previous Treatment.*—Cannon and his associates<sup>14</sup> listed 8 cases in which arsenic in the form of arsphenamine or neoarsphenamine was a causative factor. The disease in these cases followed arsphenamine dermatitis. Cannon also reported 2 patients with syphilis who were treated with neoarsphenamine and in whom arsphenamine dermatitis and the classic poikiloderma-like changes developed. One report by Nobl<sup>15</sup> listed "salvarsan" arsphenamine. Whitehouse<sup>16</sup> reported the case of a 13 year old girl who experienced "arsenic dermatitis" and, later, poikiloderma-like changes. LaRocco and Cummer<sup>17</sup> listed a case of poikiloderma vasculare atrophicans following roentgen ray therapy.

*Exciting Factors of Exposure.*—There are reports of cases in which there was a history of exposure to cold.<sup>18</sup> Zinsser<sup>19</sup> attributed the disease in his patients to injury in early life of the small blood vessels on the most exposed parts of the body. In the cases of Montgomery and O'Leary<sup>20</sup> and of Ingram,<sup>21</sup> cold intensified the erythema. No cases were reported in which exposure to light precipitated the disease or caused exacerbations.

Kindler<sup>22</sup> reported a case of the disease following severe injuries from a motor accident. Many dermatologists have expressed the view

12. Oulmann, L., in discussion on Taussig.<sup>31b</sup>

13. Hazen, H. H., in discussion on Lane.<sup>4</sup>

14. Cannon, A. B.; Karelitz-Karry, M. B., and Fischer, J. K.: Poikiloderma-Like Changes in the Skin Following Arsphenamine Dermatitis: Report of Two Cases, *J. A. M. A.* **118**:122 (Jan. 10) 1942.

15. Nobl, G.: Salvarsanbedingte Poikilodermien, *Wien. med. Wchnschr.* **85**: 1050, 1935.

16. Whitehouse: Poikiloderma, *Arch. Dermat. & Syph.* **10**:651 (Nov.) 1924.

17. LaRocco, C. G., and Cummer, C. L.: Poikiloderma Atrophicans Vasculare (?), *Arch. Dermat. & Syph.* **20**:142 (July) 1929.

18. (a) Bettman: Ueber die Poikilodermia atrophicans vascularis, *Arch. f. Dermat. u. Syph.* **129**:101, 1921. (b) Bowman, K. M., and Clark, E. C.: A Case of Poikiloderma Atrophicans Vasculare, *Arch. Dermat. & Syph.* **15**:583 (May) 1927.

19. Zinsser, in Neisser, A., and Jacobi, E.: *Ikonographica dermatologica*, Berlin, Urban & Schwarzenberg, 1910, pt. 5, p. 219.

20. Montgomery, H., and O'Leary, P. A.: Poikiloderma Atrophicans Vasculare (Jacobi)? *Arch. Dermat. & Syph.* **25**:942 (May) 1932.

21. Ingram, J. T.: Dermatomyositis and Poikilodermia, *Brit. J. Dermat.* **46**: 53, 1934.

22. Kindler, T.: Poikiloderma Atrophicans Vasculare, *Proc. Roy. Soc. Med.* **36**:619, 1943.

Lever and Crawford<sup>5</sup> stated that only cases including all three of the basic manifestations should be included in this classification. This attitude is justified until a causative organism or a pathognomonic test for Reiter's disease is discovered. However, Hollander and his co-workers<sup>6</sup> included cases of "atypical Reiter's disease" in which only nonspecific urethritis and arthritis were present without conjunctivitis. Perhaps cases could be included in which only the typical arthritis and conjunctivitis are noted. The case reported here is an example of arthritis, conjunctivitis and a keratosis-blennorrhagica-like eruption. This case obviously belongs in the group of diseases under consideration. Although there was no urethritis present and there was a history of an unproved gonococcic infection ten years previously, it is felt that the complete picture adequately conforms to the clinical conception of Reiter's disease.

#### REPORT OF A CASE

E. D., a 35 year old white man, a taxicab driver, was first seen on May 28, 1945. He stated that he had been discharged from the Army in 1942 because of arthritis. However, the history of repeated pains in the joints was too vague to be of significance. In 1935 he had suffered an attack of purulent urethritis that was presumably due to gonorrhea. This had cleared promptly and had not recurred. There was no history of previous ocular symptoms. He had dropped a heavy weight on his right big toe a year previously, and six months later an operation had been performed to remove a sequestrum.

The patient stated that about the middle of May he had noted an eruption on his scalp which soon spread to his feet and to other parts of his body. There was some febrile reaction. About two days before examination his right big toe became painful and swollen. At the same time there developed redness of the conjunctivas associated with photophobia. There was no urethral discharge during the time the patient was under observation.

On examination the right big toe was edematous, erythematous and semifluctuant. The patient appeared to be ill. His temperature was 103.2 F. by mouth. Both conjunctivas were moderately injected. His entire scalp was involved in a sharply demarcated erythematous crusted eruption. There were a number of small hyperkeratotic pustules with surrounding inflammatory areolas on the elbows, knees, ankles and soles. In addition there were a number of scattered erythematous macules with silvery scaling.

Sulfadiazine in doses of 8 Gm. daily was administered by mouth. Supportive measures were also instituted. The patient was apparently improving for a few days, but on June 4 he experienced an elevation of temperature, polyarthritis affecting mainly the knees and the ankles and an extension of the eruption. The possibility that this exacerbation represented a reaction to sulfadiazine was considered but was ruled out by subsequent developments.

5. Lever, W. F., and Crawford, G. M.: Keratosis Blennorrhagica Without Gonorrhea (Reiter's Disease?), Arch. Dermat. & Syph. 49:389 (June) 1944.

6. Hollander, J. L.; Fogarty, C. W.; Abrams, N. R., and Kydd, D. M.: Arthritis Resembling Reiter's Syndrome, J. A. M. A. 129:593 (Oct. 27) 1945.

vitamin A content of the serum was 95 international units per hundred cubic centimeters of serum and the carotene 52 micrograms. The reaction to the cephalin flocculation test was negative. The stools were normal. Roentgenologic examination of the skull revealed it to be normal.

Treatment consisted of starch baths and high vitamin diet. There was no change except for relief of the swelling of the feet and ankles. The patient was discharged on February 23.

The patient was frequently observed in the outpatient department. The skin became less pigmented and the atrophic areas larger. The itching became intense, with resulting increase of the excoriations, so that the patient was rehospitalized



Fig. 2.—The patient as he appeared one week before death, when he presented numerous areas of denuded skin which continued to ooze serous and bloody discharge without crusting. The atrophic and hemorrhagic areas became enlarged and the skin more glossy and less scaly.

on September 11. Increased vascular permeability was noted by the fact that the excoriations did not crust, but continued to ooze serum and later a bloody discharge. Hemorrhagic areas became prominent, and shortly before death large patches of the skin remained denuded and bloody (fig. 2). The bleeding was so excessive that pressure bandages were required and used until death, which occurred on Jan. 9, 1945.

*Observations at Autopsy.*—Autopsy was performed twelve hours post mortem. The report was as follows:

The patient was hospitalized on June 5 and spent four months in the hospital.

*Laboratory Findings.*—Routine studies were not remarkable. The blood count repeatedly showed a leukocyte count of 12,000 to 16,000 white blood cells with 70 per cent to 80 per cent polymorphonuclear leukocytes. Urinalyses revealed no abnormalities. Kolmer and Kahn tests of the blood elicited negative reactions. The spinal fluid on examination was also normal.

A smear of prostatic fluid obtained by massage revealed some pus but no specific organisms. The albumin:globulin ratio was consistently reversed, and at times the total was as low as 3.5 mg. per hundred cubic centimeters of blood. Tests of hepatic function revealed no abnormalities. Reactions to intradermal Frei and brucellin tests were negative. Repeated blood cultures failed to result in the growth of any organisms.

Histologic examination of material taken from lesions on the soles showed changes consistent with a diagnosis of keratosis blennorrhagica, i. e., parakeratosis, hyperkeratosis, thickening of the stratum granulosum, acanthosis, elongation of the interpapillary plugs and a superficial inflammatory infiltrate. The latter was basically lymphocytic.

*Course and Treatment.*—Penicillin administered intramuscularly in doses of 25,000 units every three hours for ten days, a total of 2,000,000 units, did not affect the disease. Salicylates were also ineffective. Two intravenous injections of oxophenarsine hydrochloride failed to alter the course. Bed rest, supportive therapy and physical therapy (heat and massage) gave some relief.

Only two things seemed to be beneficial. Repeated transfusions not only increased his strength and his blood proteins but apparently benefited the eruption and the arthropathy. The patient also received one fever treatment with a modified "blanket method." He was uncooperative, and a temperature between 103 and 104 F. by axilla was maintained for only four hours. However, on the following day a definite improvement occurred in the cutaneous manifestations, and the motion of the affected joints was increased. There was also a decrease in the pain and in the swelling. Unfortunately the patient refused further hyperpyrexial treatment.

The course of the patient was basically downhill with comparative remissions followed by acute exacerbations. The cutaneous manifestations almost disappeared on two occasions prior to the final recovery. The elevated temperature continued for over two months, often reaching heights in excess of 103 F. by mouth. The elevations in the afternoon were often accompanied by chills suggesting septicemia. He lost 60 pounds (27 Kg.) during his hospitalization. The joint involvement spread from articulation to articulation including the temporomandibular articulations and those of the elbows, wrists, hips, hands, knees and ankles. The involved joints were red, hot and tender. Motion was limited by the pain and swelling. No ankylosis developed, although the progress of the disease made me constantly fear the imminence of such a development.

The cutaneous lesions started as small pustules with inflammatory areolas. These occurred in crops. They were most evident on the legs and on the feet but occurred over all of the involved joints. The tendency of keratoses to develop over affected articulations was great. The mouth was also occasionally involved concurrently with a crop of new lesions on the skin, but these lesions would persist for only a few days. The primary pustules would soon undergo hyperkeratotic changes with the eventual development of typical pyramidal waxy

Fat and muscles. No changes were noted except for the fact that the muscle bundles appeared to be abnormally spread apart by amorphous pink-staining material.

*Anatomic Diagnoses.*—The anatomic diagnoses were as follows: poikiloderma vasculare atrophicans, with superimposed infection, interstitial myocarditis, dilatation of the right and left ventricles of the heart, benign nephrosclerosis and old pleurisy (right pleura).

#### CLINICAL COMMENT

This case, both clinically and pathologically, was truly one of a cutaneous disease presenting all the cardinal signs of the entity termed poikiloderma vasculare atrophicans. Death resulted from cutaneous toxemia. At no time did the patient have vesicles, bullae, infiltrated patches, tumors of the skin or lymphadenopathy, and the symptoms from beginning to end were cutaneous. Apparently there are cases in which poikiloderma vasculare atrophicans is an independent disease that terminates fatally. Perhaps there was an underlying cause of death in this case, but autopsy failed to reveal it. The patient had a vascular permeability, as evidenced by profuse oozing of serum. He showed no evidence of an endocrine dystrophy. During the last observation in the outpatient department, although the entire skin was affected, he did not complain of weakness or especial fatigue. The chief symptom was intense itching. It was certainly not due to embryonic defect, for the patient had no symptoms until late in life.

The only possible causative factor in this case was excessive exposure to sunlight. For the entire summer the patient frequented an enclosed bathing beach where men exposed themselves to the sun for many hours at a time. This could have been the precipitating factor in the production of the cutaneous changes. One of us (J.G.D.) has frequently visited this beach, and since observation of this patient he has examined the skin of many of the older habitués who expose their skin for several hours daily. He has noted, particularly on the legs, typical poikiloderma-like changes. In blond persons this has been noticeable on the legs, face upper part of the back, and chest. Some of these men have been frequenting the beach for as long as thirty or forty years. Practically all the older men showed some type of actinic dermatosis, hyperpigmentation, atrophy and numerous areas of telangiectasia, with scattered senile keratoses on the areas previously mentioned.

When this patient was first seen, the atrophy and pigmentation were the outstanding factors, and it was decided that the case was one of atrophia cutis idiopathica, but the brilliant red areas suggested poikiloderma vasculare atrophicans. The progress of the disease confirmed this diagnosis.

After reading Oliver's excellent review,<sup>23</sup> we decided to continue observation of this case in order to determine whether the patient later experienced signs of mycosis fungoides. Continued observations and

adherent crusts of keratosis blennorrhagica. The individual lesions spontaneously cleared in three to six weeks, but new lesions continued to appear. The eruption was unaffected by local applications, elastic adhesive bandages or large doses of vitamin A. The original eruption on the scalp disappeared spontaneously and did not recur. The conjunctivitis recurred on several occasions.

After the treatment with fever, the patient, who had been apparently moribund, started to improve. The transfusions were continued. Within two weeks the patient was up in a wheel chair and was gaining weight. Except for some residual stiffness in his hips and knees the patient was clinically well a month later. He was able to walk satisfactorily with a cane and was discharged from the hospital. There has been no further observation of this patient.

#### NATURE OF REITER'S DISEASE

The basic problem concerns the nature of Reiter's disease. Reiter<sup>1</sup> in 1916 described the occurrence of the triad of urethritis, conjunctivitis and arthritis in a single case. He isolated from the blood of his patient a spirochete which he called Spirochaeta forans; he named the disease spirochetosis arthritica. However, later investigators were unable to confirm this observation. The usual spirocheticides have been ineffective in the treatment of this disease. Neither have other suggested causative factors been confirmed. However, most investigators agree that the disease is due probably to an infectious agent.

Therefore, at the present time, Reiter's disease must be considered as a clinical entity. If one can judge from the reported cases, the initial manifestation is usually urethritis, although conjunctivitis may be the first symptom. Both of these manifestations subside in a short time, i. e., days to weeks. The arthritis is most apt to develop in the knees, the ankles and the feet. This persists from two to five months and then clears spontaneously with few or no sequelae. Diarrhea and moderate fever are often noted. The disease may recur in all three basic systems, i. e., skeletal, ocular and urologic, in one or in two of them. Rosenblum<sup>2</sup> mentioned the case of a patient who had recurrent conjunctivitis with later development of the entire triad. Therefore it seems reasonable to suppose that the disease does not necessarily affect the eyes, the urethra and the joints in all cases. Abortive examples may be present either preceding the development of the entire syndrome or as a manifestation of a recurrence.

Usually cutaneous manifestations are absent. Nonspecific eruptions such as simple erythemas, urticaria, erythema nodosum and erythema multiforme may occur but are not of diagnostic significance. On the other hand, those eruptions described as balanitis circinata and as keratosis blennorrhagica hold interest for the dermatologist.

1. Rosenblum, H. H.: So-Called Reiter's Disease, U. S. Nav. M. Bull. 44:375 (Feb.) 1945.

the skin. He expressed the belief that the collagen fibers in the corium were possibly slightly more coarse than normal, but otherwise, after careful study, there were no further changes seen. The underlying muscle in this case showed no abnormality. The nature of scleroderma was discussed by Rake<sup>37</sup> in a report of cases which came to autopsy. The outstanding change consisted of a slight degree of thinning of the epidermis, with the dermis occupied by dense scar tissue in the form of interlacing hyaline fibers and containing few cells. This hyaline connective tissue extended in strands into the subdermis between somewhat atrophied fat lobules. There was no sign of inflammation. In the smaller arteries in the dermis there were somewhat thickened walls, due to proliferation of the tunica intima and endothelium, but the lumen was not occluded. The sweat glands were small and atrophic. Elastic tissue stains showed elastic fibers to be plentiful in the connective tissue of the dermis. This feature is contrasted with the absence and destruction of the same tissue in poikiloderma vasculare atrophicans. The arrectores pilorum were hypertrophied and appeared as conspicuous bands. A section of voluntary muscle from the thigh showed shrunken hyaline and dark-staining fibers lying intermingled with fibers that were swollen, pale and apparently disintegrated. The cross striations could be seen in the shrunken fibers, but not in the swollen ones. The nuclei of the sarcolemmas around the former were approximated and appeared as nearly continuous lines; some of these fibers were tortuous and curled.

Turnbull<sup>38</sup> ascribed the changes in the skin in a case of scleroderma to inflammation, and such an interpretation has been adopted by others. In Rake's cases there was nothing that suggested an inflammatory process.

Kinney and Maher,<sup>39</sup> in a report of cases of dermatomyositis that came to autopsy, have described in detail the histologic features of this disease. In the epidermis there were atrophy and evidence of degeneration and in the dermis increased compactness, with the usually loosely woven connective tissue and elastic fibers bound together by fibrous connective tissue, much of which had a hyalinized appearance. Continuous with the dermis and extending into the underlying fat were broad sheets of tissue, which in some places had a densely collagenous character. Other cases reported in this paper presented epidermal atrophy and "balloon" cells, flattening of the papillae, edema of the dermis and an increase in fibrous connective tissue in the dermis, in which inflammatory cells were

37. Rake, G.: On the Pathology and Pathogenesis of Scleroderma, Bull. Johns Hopkins Hosp. **48**:212, 1931.

38. Turnbull, H. M., cited by Castle, W. F.: The Endocrine Causation of Scleroderma Including Morphea, Brit. J. Dermat. **35**:255, 1923; cited by Rake.<sup>37</sup>

39. Kinney, T. D., and Maher, M. M.: Dermatomyositis, Am. J. Path. **16**: 561, 1940.

Therapy (including administration of penicillin, sulfonamide compounds, arsphenamine, salicylates and colchicine) has been ineffective in modifying the course of the disease. It is suggested that fever therapy may prove of value in combating this disease. In the case reported here even one inadequate treatment resulted in immediate improvement in all of the manifestations. Recovery followed in an apparently moribund patient, and the improvement dated from that treatment. However, it is agreed that Reiter's disease is apparently a self-limited process, and the possibility of coincidental spontaneous recovery cannot be denied.

*Differential Diagnosis of Reiter's Disease, Keratosis Blennorrhagica and Psoriasis Arthropathica*

	Reiter's Disease	Keratosis Blennorrhagica	Psoriasis Arthropathica
Basic condition.....	Urethritis, arthritis, conjunctivitis	Gonorrhea, arthritis, eruption	Psoriasis, arthritis
Sex.....	Male	Male	Both
Age.....	18 to 40	20 to 50	Any
Familial incidence.....	None	None	Occasionally
Initial manifestation..	Usually arthritis but may be any	Urethritis, arthritis	Eruption
Cutaneous lesions....	Hyperkeratotic pustules, nonspecific eruptions	Hyperkeratotic pustules	Silvery scaling, pinpoint hemorrhages, etc.
Location of eruption..	Localized especially on hands, feet, penis	Localized especially on hands, feet, penis	Generalized after starting on knees, elbows, scalp, etc.
Pustules.....	Usually present in typical cases	Probably always present	Occasionally present (18.2%)
Arthritis.....	Usually knees and ankles with or without involvement of other joints	Usually knees and ankles with or without involvement of other joints	Usually starts on hands and later spreads to other joints
Ankylosis.....	None	Often	Often

The disease is probably not rare, especially in military installations. After all, Hollander and his co-workers<sup>6</sup> reported 25 cases, Rosenblum<sup>7</sup> 10 cases and Bauer and Engelmann<sup>8</sup> 6 cases. A large number of cases are never recognized and/or reported. This single report of a case is presented merely as a text for the comparison of the dermatologic manifestations of Reiter's disease with keratosis blennorrhagica and with psoriasis arthropathica.

COMMENT

The table compares Reiter's disease with keratosis blennorrhagica and with psoriasis arthropathica. The information regarding the latter two diseases is reprinted from a previous article.<sup>4</sup> On the whole, Reiter's disease with keratoses is clinically indistinguishable from keratosis blennorrhagica. However, Reiter's disease is not primarily a dermatologic entity, and keratotic cutaneous lesions occur in only a

small percentage of cases, even as keratotic lesions occur in only a small portion of the cases of gonorrhea or of gonorrhreal arthritis. When these characteristic lesions accompany Reiter's triad, the differentiation must be based on laboratory studies and on the course of the disease. One feature of importance is that Reiter's disease does not lead to permanent changes in the joints, while ankylosis commonly supervenes in gonorrhea. However, this is not helpful in the acute phase.

The differentiation of Reiter's disease from psoriasis arthropathica is usually simple as evidenced by the tabulated data. The most important differentiating features are sex, initial manifestation, location of the eruption and type of arthritis. It is not within the scope of this paper to discuss this phase, and so the reader is referred to the previous paper for further details. The case presented offered difficulties in diagnosis because the original lesions resembled those in psoriasis but became hyperkeratotic pustules after the development of the arthritis.

Therefore, the concept of Reiter's disease adequately explains the long recognized fact that "keratosis blennorrhagica without blennorrhagica" does occur. However, it exists only in a specific form, and this term cannot be adopted for all pustular and hyperkeratotic lesions accompanying arthropathies not due to gonorrhea.

#### SUMMARY

Reiter's disease is compared with keratosis blennorrhagica and with psoriasis arthropathica. The former seldom presents a picture suggesting keratosis blennorrhagica, but when it does the differentiation must be based on laboratory observations and on the course of the disease.

An atypical case of Reiter's disease, apparently favorably affected by fever therapy and by transfusions but not by administration of penicillin and sulfonamide compounds, is presented.

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# CORRELATION OF BOILING RANGES OF SOME PETROLEUM SOLVENTS WITH IRRITANT ACTION ON SKIN

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PHYSICIANS seeing patients with dermatitis appearing after contact with petroleum products are handicapped in obtaining information regarding the physical and chemical properties of these products. The wide use of nondescriptive brands and trade names and the heterogeneous nature of petroleum products make it difficult to evaluate their role in causing dermatitis. This was apparent in our studies of patients exposed to a class of petroleum derivatives often referred to as mineral seal oils.

Our purpose is to facilitate judgment of the role of petroleum products in causing dermatitis by classifying such products commonly encountered by industrial physicians and to indicate the identifying properties of the various classes.

## CLASSIFICATION OF PETROLEUM PRODUCTS

Petroleum is composed of an intimate mixture of thousands of hydrocarbon compounds, with paraffins ( $C_nH_{2n+2}$ ) and cycloparaffins or naphthenes ( $C_nH_{2n}$ ) predominating and olefins, acetylenes, aromatics and other cyclic hydrocarbons present in lesser amounts. Sulfur, oxygen and nitrogen derivatives of the hydrocarbons are present as impurities. The primary separation of petroleum into commercial products is accomplished by means of distillation, each fraction containing the major portion of all compounds having boiling points within the distillation range of the fraction. Therefore the most convenient and reliable means of identification and classification of petroleum products is by their boiling ranges. A simple classification is as follows:

*Class I.*—Class I consists of distillate products with boiling ranges below 450 F. This group includes materials commonly called naphthas, solvents, gasolines, dry cleaning fluids, paint thinners, Stoddard solvent, lacquer diluents, mineral spirits and petroleum ether.

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*Class II.*—Class II consists of distillate products with boiling ranges between 350 and 600 F. These include kerosene, long time burning oil, mineral seal oil, 300 oil, absorbent oil, engine distillate, oils used for insecticide bases, gas oils and no. 1 and no. 2 furnace oils.

*Class III.*—Class III consists of distillate products with boiling ranges above 600 F. These include light lubricating oils, spindle oils, neutral oils, transformer oils, machine oils and cutting oils.

In chart I are shown graphically the boiling range characteristics of typical petroleum products of a major oil company on the eastern seaboard, and the distillation and other test data are shown in table 1.

Other physical properties of petroleum oils are commonly reported to aid in identification and to indicate the degree of refinement. Among

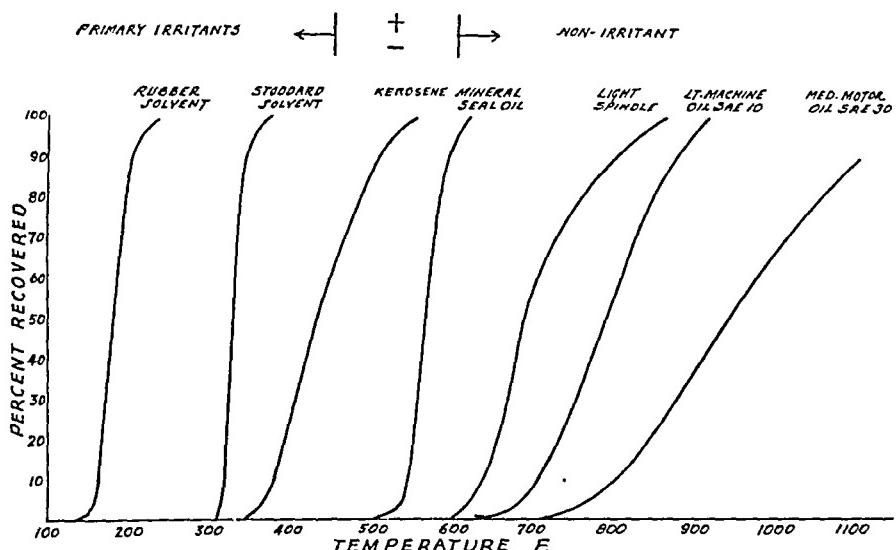


Chart 1.—Boiling ranges of typical petroleum products.

the commonest are specific gravity (A.P.I. [American Petroleum Institute] gravity is used in the petroleum industry), color, flash point, pour point and viscosity. The experienced petroleum technologist can guess as to the origin of the crude oil and the predominant hydrocarbon series present from an inspection including these characteristics. Determination of chemical make-up (hydrocarbon analysis) is a more involved and expensive procedure but would be required if a knowledge of the proportions of the constituent hydrocarbon series is desired.

For example, if two solvents have roughly identical boiling ranges, the one with the higher A.P.I. gravity (lower specific gravity) would be the more paraffinic. Other methods are in common use to supplement this simple criterion, such as aniline point, refractive index, ring number (for kerosene), viscosity-gravity constant and viscosity index. It is sufficient for the purpose of this discussion merely to mention these additional criteria.

Since this discussion deals with primary petroleum solvents, free of nonpetroleum additives, further reference to such additives is not pertinent. In this case the most useful criterion for classifying the material is the boiling range (A.S.T.M. [American Society for Testing Materials] distillation test), and this characteristic should be included in any inspection of the material under investigation.

There are few branches of manufacturing in which the use of solvents is not indispensable. In previous communications<sup>1</sup> the importance of some solvents as a cause of occupational dermatoses was emphasized.

#### CLINICAL STUDY

Our purpose is (1) to determine by patch tests variation in reaction to kerosene, mineral seal oil, spindle oil and intermediate fractions in order to determine which classes of petroleum products exert irritant action on the skin and the limits above which such irritant action would not be likely to occur; (2) by pointing out the correlation between the boiling range of the solvent and the results of patch tests, to indicate somewhat the limit of primary irritability and the possibility of individual sensitivity to products above this limit, and (3) finally to discuss the practical applications of this study.

It is generally recognized that the more viscous fractions of petroleum, free of additives, exert no irritant action on the skin. In fact, such fractions sufficiently refined serve as bases for emollients, protective creams and cosmetics. On the other hand, the more volatile fractions of petroleum have been shown to be primary cutaneous irritants and to exert a defatting action on the skin. Some writers have expressed the opinion that the irritation is entirely the result of this defatting action. However, positive reactions to patch tests with spindle oils of a boiling range and viscosity of the same order as lubricants used in emollients indicate that more is involved than action of a physical solvent, unless it is argued that these viscous oils also exert a solvent action. This point might well be worthy of investigation.

It can be stated, generally, that all products in class I (boiling ranges below 450 F.) are primary cutaneous irritants. Generally speaking, it may also be said that all products in class III (boiling ranges above 600 F.) exert no irritant action. Class II (boiling ranges between 350 and 600 F.) includes materials which give conflicting

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1. (a) Klauder, J. V.: Actual Causes of Certain Occupational Dermatoses: A Study of Five Hundred and Twenty-Seven Cases, with Special Reference to Dermatoses Due to Mineral Oils, *Arch. Dermat. & Syph.* **48**:579-600 (Dec.) 1943.  
(b) Klauder, J. V., and Hardy, M. K.: Actual Causes of Certain Occupational Dermatoses: II. A Further Study of Five Hundred and Thirty-Two Cases, with Special Reference to Dermatitis Caused by Certain Petroleum Solvents, *Occup. Med.* **1**:168-181 (Feb.) 1946.

lesions of eczematous dermatitis. Of these patients, the dermatitis of some was caused by external contact (nonallergenic) and of others there was no evidence of such cause.

*Petroleum Products Tested.*—Tests were performed with two samples of kerosene, one of paraffinic and one of naphthenic origin; four samples designated as mineral seal oil and obtained from four different refineries—(1) an East Coast refinery, from a paraffinic source; (2) a midwestern refinery, from a paraffinic source, (3) and (4) two different West Coast refineries, both from naphthenic sources—and one sample of light spindle oil of predominantly paraffinic origin. Inspection data obtained on these

TABLE 2.—*Physical Properties of Mineral Seal Oils*

	No. 1, East Coast, Paraffinic	No. 2, Midwest, Paraffinic	No. 3, West Coast, Naphthenic	No. 4, West Coast, Naphthenic
Specific gravity at 60 F.....	0.8333	0.8398	0.8631	0.8822
A. P. I. gravity at 60 F.....	38.3	37.0	31.5	28.9
Color, Saybolt.....	+16	+18	+19	-2
Flash point, F.....	275	260	—	—
Kinematic viscosity, centistokes...	4.20 at 100 F.	5.20 at 100 F.	9.36 at 100 F.	9.81 at 100 F.
Pour point, F.....	20	20	—	—
Distillation (A. S. T. M.)				
Initial boiling point, F.....	506	498	530	480
End point, F.....	607	654	667	700+
5% recovered at, F.....	537	...	552	520
10% recovered at, F.....	544	523	556	538
20% recovered at, F.....	551	532	569	555
30% recovered at, F.....	556	541	577	572
40% recovered at, F.....	559	549	584	586
50% recovered at, F.....	563	557	592	602
60% recovered at, F.....	568	566	600	620
70% recovered at, F.....	574	576	608	640
80% recovered at, F.....	580	589	618	660
90% recovered at, F.....	590	606	642	695
95% recovered at, F.....	605	...	665	...

samples are shown in table 2, and the boiling range characteristics are presented graphically in chart 2 A. Tests were also performed with 10 per cent fractions of sample I mineral seal oil (table 3). The boiling range characteristics of these fractions are discussed later.

*Patch Tests with Kerosene.*—Kerosene was tested only on persons comprising group I. All of 20 white persons reacted to kerosene from a paraffinic source: 2 had 1 plus reactions, 2 had 2 plus reactions, 10 had 3 plus reactions and 6 had 4 plus reactions. Of 14 Negroes tested, 6 reacted negatively, 7 had reactions of 2 plus or less and only 1, a mulatto, had a 4 plus reaction.

Kerosene commercially available in the eastern part of the United States is all of paraffinic origin. To determine the relative irritant

sequent study (now reported), in which a larger number of normal persons were used for patch tests, warrants the changing of this opinion that dermatitis from mineral seal oil is an allergic reaction. Evidence now suggests that such dermatitis represents a primary irritant action, appearing, for the most part, in workers whose threshold became lowered after continuous exposure.

Thirty white persons (group 1) were tested with the aforementioned four samples of mineral seal oil. The results in percentage of positive reactions were as follows: sample 1, 60; sample 2, 63.3; sample 3, 43.3 and sample 4, 12.9.

Of the positive reactions with samples 1 and 2, the 2 plus and 3 plus reactions predominated, whereas with samples 3 and 4 the predominating reactions were 1 plus and 2 plus.

Of 20 persons tested with light spindle oil, 15 per cent reacted positively, in all of whom the reactions were 1 plus.

In interpretation of these results, attention should be directed to the differences in the characteristics of the boiling range of the four samples of mineral seal oil<sup>5</sup> (table 2 and chart 2A). Sample 1 is nearest to kerosene, samples 3 and 4 are practically light lubricating oils approach-

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4. The mineral seal oil used for testing these 8 persons was sample 1, used in the study now reported. As later discussed, 18 of 30 white persons subsequently tested with this sample reacted positively. The records of the 8 controls tested in the previous report were reviewed. It was noted that in 1 of these the reaction was 1 plus and in another a questionable 1 plus. At the time of the original study these minor reactions were disregarded. In the light of present results on a larger number of persons these minor reactions assume a greater significance. This emphasizes the difficulty of evaluating minor reactions in studies with patch tests if a small number of persons is used. Apropos, from a statistical standpoint, is the question of how many persons should be given patch tests to justify a conclusion that the substance tested is not a primary irritant.

This is discussed in the following papers: Henderson, C. R., and Riley, E. C.: Certain Statistical Considerations in Patch Testing, *J. Invest. Dermat.* **6**:227-230, 1945, and Knudsen, L. F.: A Note on the Statistical Probabilities of Finding Hypersensitive Subjects in Random Samples, *ibid.* 231-232. "If no positive reactions occur in 100 subjects, the rate of positive reactions in the population is not likely to exceed approximately 2.9%, the likelihood being at the 95% level; and that if one reaction is observed in 100 subjects, the likelihood is 95% that the rate does not exceed approximately 4.5%."

Error of judgment was more inherent to ignoring the two minor reactions in the group of 8 persons tested than in the small number employed. We do not believe that patch tests performed on a larger number of persons than were employed in the study now reported would affect the validity of our conclusions, although the percentage of incidence of positive reactions would be somewhat changed.

5. The quality of mineral seal oil apparently varies among different refiners. There is no accepted trade standard of what constitutes mineral seal oil. Federal specification VV-0-391, Oil; Illuminating (mineral seal oil with a boiling range of 300 F.), sets no limits for boiling range or viscosity, placing primary emphasis on burning characteristics in a lamp.

ing spindle oil and sample 2 is intermediate. These petroleum products are on the borderline between volatile solvents and lubricants. The greatest percentage of positive reactions occurs with the samples (1 and 2) having the lowest boiling range. The higher incidence of positive reactions with these samples can be attributed to their proximity to the boiling range of kerosene. The result is what would be expected in a blend of kerosene and lubricating oil, which mineral seal oil is to all intents and purposes.

The proportion of kerosene in the blend correlates primary irritant action. Conversely, mineral seal oil samples 3 and 4 are blends containing relatively small proportions of kerosene. Their irritant action approaches the relative immunity of lubricating oil (light spindle oil).

We also conducted studies by patch tests with a petroleum solvent obtained from a cracking process employed in obtaining high octane gasoline. The boiling range of this solvent corresponded essentially to that of kerosene, but its chemical composition reflected a high aromatic content approaching coal tar distillates. This solvent would have a high solvency for many materials for which the solubility in ordinary kerosene would be limited. Patch tests on normal persons uniformly gave 4 plus reactions. This greater irritant action suggests that solvency or defatting action is intimately associated with cutaneous irritation. The greater irritant action of this solvent (of high aromatic content) did not correlate with the boiling range. The correlation of boiling range with irritant action applies to the paraffinic type of petroleum products and not to naphthenic or highly aromatic products whether derived from petroleum or other sources.

Although patch tests were not performed with petroleum solvents of boiling ranges below those of kerosene, we believe, from clinical experience, that such solvents, in contrast to kerosene, would produce more uniformly severe reactions and that, in contrast to mineral seal oil, all persons would react.

It is of interest to note that cutaneous reaction to paraffinic kerosene varies only qualitatively. As the boiling range increases, the reaction varies both quantitatively and qualitatively and becomes considerably attenuated in the boiling range of light spindle oil.<sup>6</sup>

Tests with four samples of mineral seal oil and with light spindle oil were performed on industrial workers.

6. From clinical experience, prolonged exposure to light spindle oil does not suffice to cause dermatitis. This is in contrast to mineral seal oil of boiling ranges corresponding to samples 1 and 2. Wedroff and Dolgoff (*Zur Frage der Pathogenese der Ölacne, Arch. f. Gewerbeopath. u. Gewerbehyg.* 6:428-436, 1935) concluded from their observation of workers exposed to mineral oil (lubricating oils) of the naphthenic type that the incidence of eczematous dermatitis was no greater than its incidence in general. In Hopf's (*Ueber gewerbliche Oelschädigungen der Haut, Aerztl. Sachverst. Ztg.* 43:229-241, 1937) observation, dermatitis from mineral oil (lubricating oils) was not common except in eczematic persons.

The dermatitis (usually on the hands and forearms) of the workers in group 2 appeared after variable periods of exposure either to mineral seal oil or to other petroleum solvents such as kerosene or Stoddard solvent. In some the solvent was not identified; in others the properties of the mineral seal oil were not known. The interval between the first exposure and onset of dermatitis was variable—weeks (infrequently), months, usually one year or longer or, in some, as long as twenty to thirty years. Conspicuous among these workers were pressmen and their helpers who clean printing presses with a petroleum solvent of a boiling range of kerosene or lower.<sup>1b</sup> The number of workers tested with each sample varied from 15 to 39.

The results in percentage of positive reactions were as follows: sample 1, 92.3; sample 2, 100; sample 3, 66.6; sample 4, 47.3, and light spindle oil, 72.3. Of positive reactions with samples 1 and 2, the 2 plus and 3 plus reactions predominated.

The smaller percentage of positive reactions to sample 4 compared with that to spindle oil is a discrepancy. Sample 4 of mineral seal oil approaches the boiling range of light spindle oil; yet the percentage of positive reactions to patch tests was less than that of spindle oil. This discrepancy may be related to the hydrocarbon composition of these oils. In these persons a lowered threshold to paraffinic oils, of which light spindle oil is an example, has developed. Samples 3 and 4 are naphthenic. Therefore the reaction to these oils is nearer to that of the normal skin as in group I.

*Patch Tests with 10 Per Cent Fractions of Mineral Seal Oil.*—Since samples 1 and 2 of mineral seal oil produced a large proportion of positive reactions in persons comprising groups I and II, an effort was made to determine which part of their boiling range was chiefly responsible for this high incidence. A portion of sample 1 was refracted by distillation through a fractionating column, being separated into 10 per cent fractions. Each fraction was inspected in the laboratory, and the characteristics of the ten fractions are shown on table 3 and chart 2B. It should be noted that the first five fractions (50 per cent of mineral seal oil) fall largely within the boiling range of kerosene. Fractions representing 51 to 90 per cent fall between the end point of kerosene and the initial boiling point of spindle oil, while the last 10 per cent falls entirely within the boiling range of spindle oil.

Patch tests were performed with these ten fractions on 35 white persons (group I) and on workers with dermatitis caused by solvents (group II). The number of workers (group II) tested with each fraction was 45. The results in percentage of positive reactions (1 to 4 plus), starting with fraction 1 and in the order written to fraction 10, were as follows:

Group I: 100, 100, 82.8, 80, 77.7, 60.0, 57.0, 40.0, 22.7, 11.4.  
Group II: 100, 100, 100, 95, 92.5, 90.2, 90.2, 87.8, 84.8, 70.7.

In both groups the incidence of positive reactions was greatest in the fractions within the kerosene range and least in the fractions approaching lubricating oil.<sup>7</sup> The degree of positive reactions was consistent with the incidence. Three plus reactions in tests with the first five fractions predominated, whereas 2 plus and 1 plus reactions predominated in tests with fractions 6 to 10. The observation that irritant action on the skin of the paraffinic type of petroleum products decreases as the boiling range increases is similar to observations on solvent action, which likewise is in inverse ratio with the boiling range. Since the results obtained with highly naphthenic and highly aromatic products do not correlate with the results obtained with paraffinic products, the correlation of boiling range cannot be applied to these materials. In view of the higher solvency of the naphthenic and aromatic solvents, it is possible that the increased irritant action reflects a heightened defatting action. There is also the possibility that it is a reflection of chemical toxicity.

The varying tolerance of the normal skin as noted in patch tests with paraffinic kerosene was again apparent with the ten fractions in the study of persons in group I. The individual variation was considerable; it ranged from 1 plus to 2 plus reactions to only the first two or three fractions to a varying degree of positive reactions to all ten fractions (4 patients).<sup>8</sup> This variation could not be correlated with complexion. Not all persons who reacted to many or to all of the ten fractions were blonds; conversely, not all who reacted to only the first few fractions were dark complexioned.

Patch tests with the ten fractions were also performed on 18 Negroes. The incidence of positive reactions was considerably less than that of white persons. Frequently there was no reaction. (It is possible that slight erythema could not be seen on the darker-skinned Negroes.) Many had 1 plus reactions only to the first two or three fractions. The most pronounced result (in a mulatto) was 1 plus and 2 plus reactions up to fraction 6.<sup>9</sup>

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7. A few workers included in group II whose dermatitis was presumably caused by petroleum solvents reacted only to the first four or five fractions. This apparently opposed solvent as a cause; at the same time such reaction was not that of an eczematic skin. An allergic causation of the dermatitis in these patients was therefore suggested, but it could not always be proved. If the dermatitis was caused by solvents, apparently then the skin of the back, the site of the patch tests, did not share in the lowered tolerance.

8. This emphasizes how relative is the term "primary irritant." What should be the concept of a primary irritant? Should it connote the reaction of an individual or reaction of all persons tested? Definitions in vogue envisage one or the other of these meanings. The difference, of course, is relation to what is the "normal" reaction of the skin. The word "normal" itself has been so much abused that some teachers request students not to employ it.

It is to be noted that the percentage of positive reaction (but not the degree of reaction) to the ten fractions and also to the mineral seal oils (samples 1 to 4) and to spindle oil was appreciably greater in persons comprising group II than in white persons in group I. This evidences a lower tolerance not only to the solvent which gave rise to the dermatitis but to paraffinic petroleum products of higher boiling range, extending into the range of lubricating oils.<sup>10</sup>

As discussed in the foregoing paragraphs, there is evidence that lowered tolerance to paraffinic products is not reflected in a comparable degree to naphthenic products (samples 3 and 4 of mineral seal oils) of the approximate boiling range. This suggests a chemical specificity.

Since the degree of positive reactions was not greater than that observed on normal persons, an allergic hypersensitivity can be excluded. In order to determine whether the lower tolerance was specific for petroleum products or existed for all external irritants, an expression of the eczematic skin, the following study was performed.<sup>11</sup>

Eighteen patients in group II who reacted to all or to almost all the ten fractions were given patch tests with the following eczematogenous noxae: 50 per cent turpentine in olive oil, 5 per cent solution of formaldehyde, 0.5 per cent potassium dichromate, tincture of iodine, 5 per cent ammoniated mercury in petrolatum, 1 per cent ammonium fluoride and 1 per cent sodium arsenate. The dermatitis of these patients varied in degree; it affected only the hands in some; in others it affected the hands, forearms and arms. The reactions to the eczematogenous noxae were variable, ranging from reaction to only a few of the noxae to reaction to the majority. The percentage of positive reaction to each noxae varied from a minimum of 27 per cent (tincture of iodine) to 75 per cent (0.5 per cent potassium dichromate).

As a control study, 20 patients with eczema (group III) were given patch tests with the ten fractions and also with the aforementioned eczematogenous noxae. Eleven of the 20 patients reacted to all ten fractions. Negative reactions were obtained only with fractions 8, 9

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9. These observations are consistent with knowledge that the skin of Negroes is less susceptible to external irritants. Dr. Sidney Repplier, of the Curtis Publishing Company, informs us that the incidence of dermatitis from solvents used to clean printing presses is considerably less among the Negro employees.

10. It would be of interest to note at what point in the range of viscous petroleum products this lower tolerance is no longer apparent.

11. One phase of our purpose was to exclude possibility of impaired function of the skin in combating defatting action of solvents, comparable to impaired function to neutralize alkali. As a result of his studies, Burckhardt (*Beiträge zur Ekzemfrage: die Rolle des Alkali in der Pathogenese des Ekzems speziell des Gewerbeekzems*, Arch. f. Dermat. u. Syph. **173**:155, 1935; *Das Maurerekzem [Eine experimentelle und klinische Studie zur Ekzemfrage]* ibid. **178**:1, 1938) attributed such impairment as a cause of dermatitis due to alkali. He designated it toxic hypersensitivity in contrast to allergic hypersensitivity.

the article of work or containers such as ink and paint cans. Usually small parts were immersed by hand into a solvent without the use of gloves. This was done by machinists, machine operators and a variety of other workers." For this purpose mineral seal oil may suffice or a mixture of kerosene and mineral seal oil.

*Practical Application of Patch Tests with the 10 Per Cent Fractions.*

—It is well known that a patch test performed with a petroleum solvent with a low boiling point is of limited value. By virtue of its primary irritant action a positive result can be predicted. Our studies suggest that a solvent with the boiling range of kerosene or lower will uniformly give a positive reaction to a patch test.

Patch tests performed with a number of solvents having ascending boiling ranges, comparable to the ten fractions employed in this study, are a means of determining the tolerance of the skin to paraffinic petroleum solvents: Such a series of tests has a practical application, since it is a means of selecting persons whose cutaneous tolerance to solvents is high. A high tolerance would be indicated by reactions only to the first two or three fractions, in contrast to all or to the first seven or eight. A less accurate way of determining tolerance is a single patch test performed with kerosene. We observed that reaction to kerosene varied from 1 to 4 plus. The degree of reaction to kerosene corresponded, in the majority of persons tested, with the number of positive reactions obtained with the ten fractions.

If patch tests with the ten fractions were employed in selecting persons for work entailing exposure to solvents, it would doubtless eliminate the workers in whom after short exposure dermatitis develops. Such tests, however, would not prevent dermatitis apparently caused by lessened tolerance inherent to prolonged exposure and to an increased degree of exposure.

As discussed in the foregoing paragraphs, positive reaction to all or almost all the ten fractions is characteristic but not diagnostic of dermatitis caused by petroleum solvents. On the other hand, positive reactions to only the first one half or less of the ten fractions is evidence against such cause of dermatitis. This is illustrated in the following case:

In a man operating a grinder exposing his hands and forearms to soluble cutting oil, there developed dermatitis affecting these areas. A solvent in the oil was suspected. No accurate information was available as to its composition. Its physical appearance was that of a light spindle oil. Reactions to patch tests with this oil and the four samples of mineral seal oil were negative. The reaction to the ten fractions was as follow:

Numbers										
1	2	3	4	5	6	7	8	9	10	
1+	1+	1+	—	—	—	—	—	—	—	—

This study evidenced a high degree of tolerance to petroleum solvents, opposing solvent causation of the dermatitis, and excluded an allergic reaction to the oil.

5. Cutaneous reaction to kerosene of naphthenic origin and to a solvent of high aromatic content obtained from a cracking process employed in obtaining high octane gasoline was much greater than that of solvents of paraffinic origin with the same boiling range. With the former products defatting action or chemical toxicity might be the cause of increased irritant action.

6. The amount of individual tolerance to petroleum oils and solvents can be determined by patch tests with ten distillation fractions with different boiling ranges, extending from that of kerosene to that of light spindle oil.

7. Dermatitis caused by petroleum solvents is regarded as the expression of a nonspecific sensitivity comparable to dermatitis from exposure to other eczematogenous noxae.

8. Practical application of this study is discussed.

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#### ABSTRACT OF DISCUSSION

DR. LOUIS SCHWARTZ, Bethesda, Md.: Dr. Klauder and Mr. Brill are to be congratulated for their fine paper. Such experimental work should be encouraged. First, I want to make clear that mineral seal oil is a cutting oil used for light cutting operations. They have proved by experiments what my colleagues and I have observed in industry and taught to our classes from another viewpoint, namely, that the irritant properties of various petroleum distillates are directly proportionate to their fat solvent properties and that the latter are inversely proportionate to their viscosities, all other factors being constant. The paper brings out the fact that even the last of the ten fractions, which is an oil, caused 11.4 per cent of reactions in the control group, showing that even the oily fractions have a primary irritant action on certain types of skins. We have found that this irritant action occurs mostly on dry skins or senile skins, which cannot rapidly replace the fat which the oil takes out. For this reason we state that mineral oils should not be used as ointment bases, either cosmetic or medicinal, on dry skins and that they make good bases for oily skins.

The last of the ten fractions caused reactions on 70.7 per cent of the workers who had dermatitis and worked with these oils. This high incidence of positive reactions to patch tests is explained by the fact that these workers showed by their dermatitis that among them predominated the types of skin which cannot stand defatting, namely, dry skin or senile skin. The 29.3 per cent of the patients with dermatitis who had no reactions to the patch tests either had dermatitis from some of the additives in the oils with which they worked or did not have occupational dermatitis, or their dermatitis may have been caused by the accumulation of the continued action of large quantities of the oils occupationally encountered, conditions not present in the patch tests.

The increased susceptibility of dry skins to the action of fat solvents can be regarded as a hypersensitivity due to an anatomic and physiologic defect of the skin and not as an allergy. An allergy of the skin denotes to me a change in the reactivity of the body fluids or cells induced by exposure to an allergen, which manifests itself by a dermatitis on a reexposure to the same or a similar allergen.

the action of the various petroleum distillates, but he cannot stop time and prevent a young worker with such a skin from becoming an older worker with a vulnerable skin.

DR. HARRY J. TEMPLETON, Oakland, Calif.: This scientific investigation into a relatively unexplored field is of the excellence that one expects and always gets in Dr. Klauder's papers. It is unfortunate that the time allotted did not permit him to give many details which we who were permitted to read the paper obtained.

When one first reads this paper and looks at all the charts, it seems rather technical, but further study shows its great practicability. For example, manufacturers might be able to reduce the incidence of oil dermatitis or entirely eliminate it by changing from some of the light oils of low boiling point and higher irritability to some of a higher boiling point and a low irritability, or they might change from the irritating oils of the naphthenic series to the less irritating oils of the paraffin series. These two points alone make the paper practical.

I doubt somewhat the actual practical value of preemployment routine patch tests of applicants with the various fractions of mineral seal oil. In the first place, I do not think that employers will go to the trouble of doing this.

In the second place, I think that there is at least a theoretic danger of sensitizing patients to certain fractions. From my own experience, I should warn against the use of the full strength oils of the lower boiling range in patch tests. Earlier in my experience, I blistered some patients unmercifully by so doing and even produced second degree burns with some of the fractions, such as Stoddard solvent and kerosene.

During the war, my colleagues and I here in the San Francisco Bay district saw a great deal of industrial dermatitis in general and oil dermatitis in particular, as did all dermatologists. Because of this great problem, several committees began the study of industrial dermatitis and oil dermatitis. One was from the United States Public Health Service, one from this Section on Dermatology of the American Medical Association, and one from the American Dermatological Association.

Having served on Dr. Schwartz's Committee of the United States Public Health Service, I can testify to the valuable work that he and his group in Washington are doing on this problem of oil dermatitis. This would be expected when one remembers that he has dermatologists, physicists, mycologists, chemists and botanists at his command and that he and his staff have the utmost experience in the field work, which goes on right out into the factory. However, as I have sat in on those conferences, I have been impressed by the fact that the knowledge that his group gains is not sufficiently widely disseminated, and it occurs to me that there ought to be a closer relationship—a liaison of some kind—between the committees for the United States Public Health Service and the committees from the American Medical Association and the American Dermatological Association, which are composed of the practical dermatologists throughout the country who are doing a great deal of the industrial dermatology. I make it as a suggestion that these committees pool their findings; otherwise something will be lost.

DR. J. V. KLAUDER, Philadelphia: The percentage of positive reactions to patch tests performed with fractions 1 to 10 included all reactions from 1 to 4 plus. The figures that Dr. Schwartz quoted, percentage of positive reactions to the last fraction, comprised all 1 plus reactions. It is to be noted that this reaction was produced after twenty-four hour contact of the patch; since the material

## CUTANEOUS DIPHTHERIA

*Two Unusual Cases with Eruptions Resembling Lymphogranuloma Venereum and Ectodermosis Erosiva Pluriorificialis*

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DESPITE the high frequency in China of diphtheritic infections of the upper respiratory tract, not a single case of cutaneous diphtheria has hitherto been reported. This fact may be understood better if one considers the large number of clinical manifestations which are caused by the bacilli. On the other hand, the importance of cutaneous diphtheria has been little stressed in the past on account of its rare occurrence, and because one seldom observes the typical false membrane type of disease on the skin. Moreover, it should be emphasized that the occurrence of a great many varieties makes even more difficult recognition at first glance of the true nature of the eruption. It is, however, of paramount importance, especially from an epidemiologic point of view, to suspect cutaneous diphtheria whenever a pustular eczematous ulcerative process does not yield to ordinary treatment, and when lesions show a preference for certain localizations.

### CLINICAL MANIFESTATIONS

The clinical picture is varied, and among the many varieties described the false membrane type is still known as the most characteristic. To attach a diagnostic significance principally to the formation of pseudo-membranes is erroneous, as other cutaneous diseases also produce pseudomembranes without having any relationship to diphtheria. Wound diphtheria, as a postoperative complication, is dreaded by all surgeons. This, like other diphtheritic infections of the skin, is difficult to diagnose without bacteriologic investigation, unless postdiphtheritic complications (palsy, for example) give a warning sign. Otherwise, the granulating wounds do not always show suspicious changes such as formation of dirty-looking adherent membrane, the removal of which is difficult and is followed by profuse bleeding. Moreover, the wound may not show any increased inflammatory reaction, and, despite this, along the necrotic undermined borders is a steady spreading of the ulceration. The ulcerative type has been fairly well recognized, and one should suspect diphtheria as a cause when punched-out ulcers appear suddenly, espe-

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cially in children. Intertriginous localization makes such a suspicion even more justified. The eczema-like type ranges next to it in frequency. In children the combination of retroauricular eczema with rhinitis, conjunctivitis and otitis should always be thought of as a diphtheritic syndrome. In other instances perioral and periocular eczema is associated with conjunctivitis and rhinitis, a combination highly indicative of a diphtheritic cause. Diphtheritic eczema may be localized in the genital region or, in rare instances, may affect the external auditory canal alone. Impetiginous, impetiginous-eczema-like, ecthymatosus, vesicular and bullous types have also been reported. Among the rarer types are eruptions resembling dermatitis herpetiformis, tumor and abscesses.

During the years 1938 to 1941 closer attention has been paid in the clinic of the National Medical College of Shanghai to cutaneous diphtheria. Among 18,644 new cases of cutaneous disease (from July 1938 to September 1941) 9 cases (0.38 per cent) have been recognized culturally, and, also, the virulence test proved in all instances a high degree of pathogenicity. Among the 9 cases virulent bacilli from the throat and from the nose could be cultured in only 1 instance. Six were of the ulcerative variety, 1 was impetiginous, 1 was of the ecthyma type and 1 presented lesions in a child which clinically could hardly be differentiated from lymphogranuloma venereum, an infection which rarely occurs in children. The ninth case was observed in the European Refugee Isolation Hospital and presented a sudden appearance of periorificial ulcerations, a picture rather suggestive of ectodermosis erosiva pluriorificialis.

#### REPORT OF CASES

CASE 1.—W. C. H., a girl of 4, was brought in by her parents on Dec. 24, 1938 with a history of masses in both inguinal regions for nearly three months. The masses steadily increased in size and were painless. They were incised two months previous to her visit, when a thick whitish material was evacuated. Her parents noticed a small ulcerative lesion between the labia majora one month after the onset of the inguinal swelling, which disappeared in one week's time. It broke out again and remained for the two months. Swelling throughout the external genitalia was present for the two months. The patient was well developed and well nourished and did not appear to be sick. Local examination revealed a purplish red swelling of the vulva with sensation of resistance on palpation over the surrounding tissue. The inner surfaces of the left labium majus and labium minus were irregularly ulcerated, with a slight amount of discharge. Discharging sinuses and ulcers were found in the inguinal regions. The patient's father had had a bubo in the left inguinal region four years before, but his reaction to the Frei test was doubtful, and that of her mother was negative. Laboratory data showed the following blood count: red blood corpuscles 4,800,000; white blood corpuscles 23,600, with 76 per cent polymorphonuclear leukocytes, 18 per cent small lymphocytes, 2 per cent large lymphocytes, 2 per cent monocytes and 2 per cent myelocytes. Smears and cultures, except hemolytic streptococci, did not suggest pathogenic organisms. Reactions to repeated Frei tests (three antigens) were negative. Treatment consisted of sulfanilamide administered orally and compresses of lotion of

lead acetate administered locally, under which the patient showed slow but steady improvement. The affected parts became soft, and the edema subsided substantially. On account of the unsatisfactory therapeutic result cultures were made for diphtheria bacilli with positive results. Diphtheria antitoxin (5,000 international units) was given immediately, after which the child disappeared from observation until a return visit on March 9, 1939. On this visit the child's temperature was 38.3 C. (100.94 F.), and inguinal and vulval lesions were about the same. The tonsils were enlarged and congested. The patient had a high temperature and died that very night (at home), probably of toxemia.

CASE 2.—Mr. F. F. (fig. 1), a 30 year old German refugee, came to the hospital on Oct. 28, 1940 in a feverish condition lasting two days. Before the onset of the fever he had a painful sensation in the left inguinal region and a sort of tension in the vicinity of the mouth. On November 3, I was called in consultation, and on examination I observed in the left inguinal region a 10 by 4 cm., irregularly outlined,

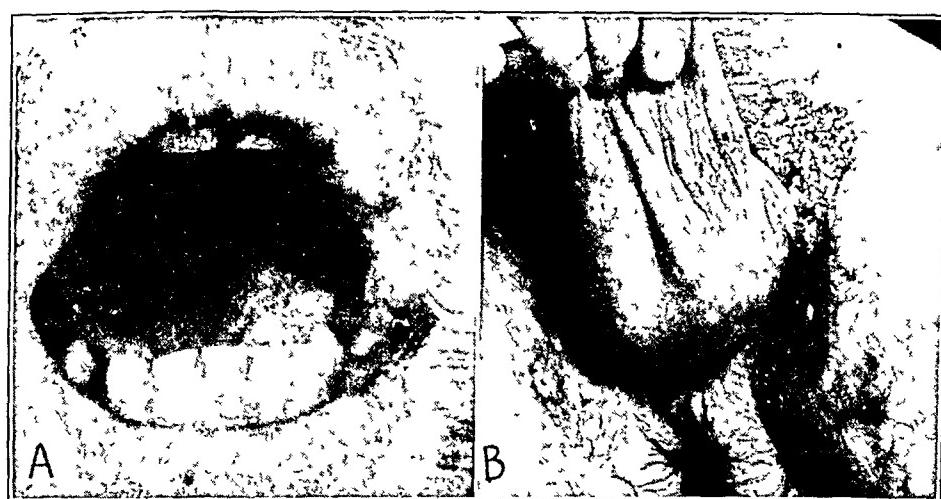


Fig. 1.—A, a bean-sized ulcer in the vicinity of the left angle of the mouth. B, extensive ulcerations in the right inguinal region and smaller ulcers on the scrotum and in the right crural region.

shallow sore, which was covered with bloody crusts. On several places on the scrotum were bean-sized lesions, and on the right side of the thigh were several shallow ulcerations with partly undermined borders. On the lower lip in the vicinity of the left angle of the mouth was a painful ulcer the size of a horse bean, which was covered with a fibrinous exudate. In the vicinity of the left nostril a similar lesion was found. In view of the sudden onset, with the initial temperature of 37.8 C. (100.04 F.) reaching 38.2 C. (100.76 F.) three days after admission and, furthermore, with the sudden appearance of periorificial pseudomembranous lesions, the possibility of ectodermosis erosiva plurioreficialis was considered. A blood count showed 4,700,000 red blood corpuscles and 7,600 white blood corpuscles. The Wassermann and the Kahn reaction of the blood were negative. A blood culture for diphtheria bacilli was negative. Smears were made from the lesions which revealed a palisade-like arrangement of diphtheroid bacteria, which the culture and the virulence test proved to be of the virulent diphtheritic type. The same observations were made and the same results were obtained from the nose and from the throat on November 17 and on December 6. A biopsy was made, and the histo-

logic examination revealed the following (fig. 2): The epidermis and part of the cutis were replaced by an ulcerative process and were bordered by acanthotic epidermis. The floor of the ulcer was covered with necrotic material, leukocytes and cellular and nuclear detritus. There was, furthermore, a diffuse fibrinous exudate which extended to the cutis. The collagenous fibers were loosened, and, besides numerous leukocytes, there were a great many red blood corpuscles around dilated blood vessels.

The treatment consisted of local application of antidiphtheritic serum and of azosulfamide ointment and administration of 6,000 units of diphtheria antitoxin. Under this treatment the sores became cleaner, and healthy granulations replaced

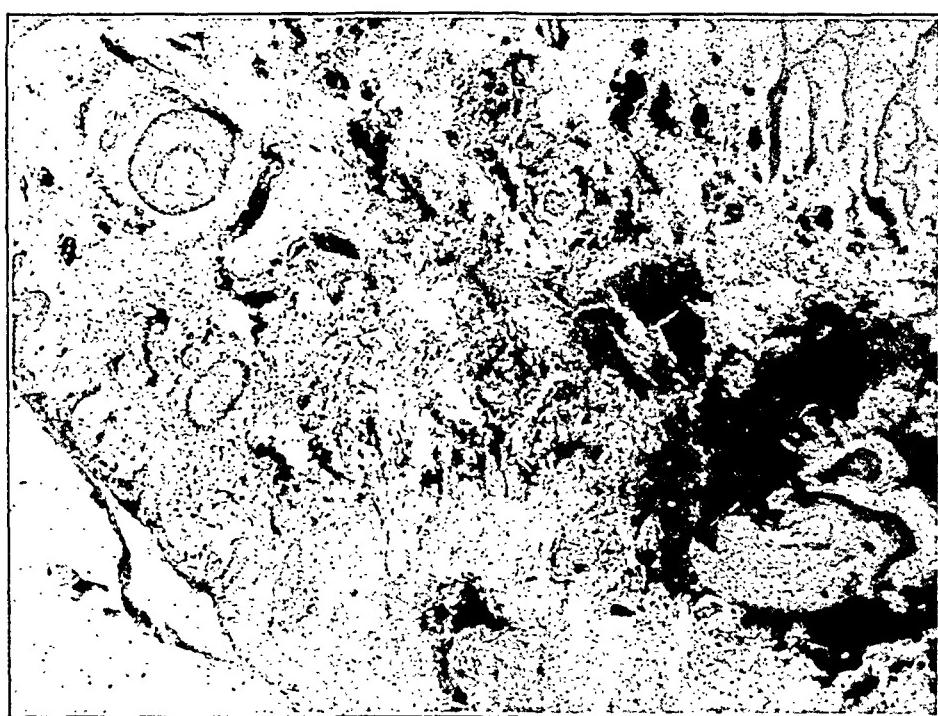


Fig. 2.—Showing the necrotic process involving the subcutis with deeply staining fibrinous exudate and cellular debris.

the dirty membrane and the ulcerations. Complete recovery was achieved on November 30. Cultures from the throat and from the nose done on December 2 proved to be negative.

#### DIFFERENTIATION OF THE DIPHTHERIA BACILLI AND THE PSEUDODIPHTHERIA BACILLI

Although from the staining (bipolar bodies, palisade-like arrangement of bacilli) one can gain certain information of the character of diphtheria bacilli, the culture, the biochemical reactions and the virulence test are more exact. The method of Martin and Loiseau<sup>1</sup> is not quite so reliable as claimed, because often there is only a surface growth on dextrose agar stab cultures, and yet the growth may prove to be diph-

1. Cited by Calmette, A.; Boquet, A., and Nègre, L.: Manuel technique de microbiologie et sérologie, ed. 3, Paris, Masson & Cie, 1933.

theria bacilli. This is borne out by my experience. The Costa-Troisier method is based on the acid formation of diphtheria bacilli on dextrose agar, whereby with the help of an indicator colonies of diphtheria bacilli appear rose, whereas colonies of pseudodiphtheria remain grayish. This method proved reliable in my cases. Besides the routine virulence test I investigated a method, communicated personally by Prof. H. Raubitschek, which consists of the following procedure: From a twenty-four hour diphtheria culture a saline suspension is made (5,000,000 organisms in 1 cc.) from which 0.5 cc. is mixed with 0.5 cc. of isotonic solution of sodium chloride, and in another tube 0.5 cc. bacterial emulsion is mixed with 0.5 cc. diphtheria antitoxin. Both tubes are kept for two hours in incubators at 37 C. after which 0.2 cc. from each suspension is injected intradermally into the right and the left abdominal wall respectively. When there was diphtheritic infection the injection of the bacterial-saline mixture would produce severe hyperemia and necrosis after twenty-four to forty-eight hours, but no reaction on the side where the antitoxin-bacterial emulsion was injected. This can be confirmed by my experiments, but in addition it should be remarked that animals tested with virulent diphtheria bacilli died after thirty-six hours. In instances of pseudodiphtheria both sides would produce hyperemia and necrosis. From a practical point of view, the determination of virulence should be demanded in order to rule out pseudodiphtheritic bacilli infections, 50 per cent of which are present on the normal skin. Eller and Kest<sup>2</sup> claimed that diphtheria bacilli "have a varying virulence for different species and even for the same species." According to these authors the degree of virulence may be variable, so that the virulence test may show only the degrees of virulence but does not differentiate true diphtheria from pseudodiphtheria.

From an epidemiologic point of view it is necessary to adhere to a strict differentiation between diphtheria bacilli and pseudodiphtheria bacilli, and for that reason attention should be drawn to the clinical picture of cutaneous diphtheria. The purpose of the article was not so much to describe two rare types of cutaneous diphtheria as to emphasize the commoner forms of the disease. Cutaneous diphtheria has been the cause of serious spreading of diphtheria of the throat, because it has not been recognized in time. One of the most striking examples is the case reported by Boas<sup>3</sup> of impetigo-like conditions in a 1 year old child, which later proved to be diphtheria, and which infected in the same ward 4 other children, 3 nurses, 1 male attendant and 1 female attendant. When one observes in Shanghai the many instances of

2. Eller, J. J., and Kest, L. H.: Eczema of the Ear Associated with a Diphtheria-Like Organism, Arch. Dermat. & Syph. 44:1020-1022 (June) 1940.

3. Boas, L.: Diphtheria der Haut, Zentralbl. f. Haut- u. Geschlechtskr. 33: 27, 1930.

innocently acquired cases of syphilis among children, one can well imagine the role cutaneous diphtheria may play in spreading the disease, especially since diphtheria bacilli can remain virulent on dead material for more than eighteen months.

#### COMMENT

The 2 reported cases are undoubtedly unusual in their clinical appearances. Although from tumor-like swellings virulent diphtheria bacilli have been isolated by Müller<sup>4</sup> from the pus of an inguinal abscess, not a single instance is on record of similar clinical manifestations of lymphogranuloma-venereum-like diphtheria. One of the commonest and most characteristic symptoms in diphtheria of the vulva in children, the retention of urine, was absent in my case (case 1) as was the usual bloody discharge. The absence of these symptoms was sufficient cause not to suspect diphtheria bacilli. Therefore, there was ground to consider lymphogranuloma venereum. However, thorough investigation proved the infection to be caused by diphtheria bacilli.

The second case bore all the characteristics of ectodermosis erosiva pluriorificialis, a disease with an infinite variety of clinical symptoms but characterized by sudden rise of temperature, rapid appearance of perioral and perianal erosions and ulcerations often coupled with conjunctivitis, rhinitis and diphtheroid stomatitis. While I do not propose to enter into discussion of the cause of ectodermosis erosiva pluriorificialis here, it is my contention that this syndrome suggests a bacterial intoxication, which may be in some rare instances caused by diphtheria bacilli. The only case which bears some similarity to this one is reported by Santori,<sup>5</sup> who described a "rather unusual" appearance of multiple intertriginous pseudomembranous ulcerations in the genital and in the retroauricular region, all of which proved to be caused by virulent diphtheria bacilli.

#### CONCLUSION

Two unusual types of cutaneous diphtheria are reported. One resembles lymphogranuloma venereum and the other ectodermosis erosiva pluriorificialis. In one case the upper respiratory tract contained diphtheria bacilli, and in the other it did not. The isolated bacilli were highly virulent.

Attention is drawn to the importance of early recognition of cutaneous diphtheria from an epidemiologic point of view.

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4. Müller, J. E.: Seltene durch den Diphtheriebazillus hervorgerufene Erkrankungen, Deutsches Arch. f. klin. Med. **109**:583, 1913.

5. Santori, G.: Primäre Hautdiphtherie mit vielfachen Herden, Dermat. Wochenschr. **110**:367, 1941.

## ECZEMATOUS SENSITIZATION

A Review of Its Immunologic Properties and Some Speculations  
as to Its Nature

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WHEN the living organism comes into either external or internal contact with a foreign substance a variety of alterations may ensue. One of these is a subtle change in the body's economy, which is not immediately manifest, so that on again meeting the substance the organism presents an altered reactivity to it. This altered reactivity is what is termed the allergic reaction, and when this state of altered reactivity has developed, the organism is said to be sensitized. There are, however, different possible varieties of sensitizations of which at least three appear to be distinct immunologic entities. These are: (1) the anaphylactic (of which I regard the atopic as a part), (2) the tuberculin or bacterial and (3) the eczematous variety. It is with this last variety that this paper deals.

### NATURE OF THE SUBSTANCES WHICH YIELD ECZEMATOUS SENSITIZATIONS

In considering the nature of the substances which elicit eczematous sensitizations it seems necessary to distinguish between eczematous sensitizations which arise spontaneously and those which are deliberately produced. The materials which yield eczematous sensitizations spontaneously are almost legion in number, as any practicing dermatologist knows, but the substances with which one can produce an eczematous sensitization deliberately are far more restricted in number. In both cases they are relatively simple compounds, usually of known chemical configuration. In fact, when the actual eczematous allergen has been isolated from complex mixtures, such as the juices of the Chinese primrose or poison ivy, the allergen has turned out to be a relatively simple compound, such as primin (empiric formula:  $C_{14}H_{18}O_3$  or  $C_{14}H_{20}O_3$ ) in the primrose and a compound closely related to n-penta-decyl catechol in poison ivy. There appears to be a definite correlation between the capacity of substances for regularly causing eczematous

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Based on a talk given at the fifth annual meeting of the American Academy of Dermatology and Syphilology in Cleveland, Dec. 11, 1946.

ously developing sensitizations it is practically impossible to study this question. We therefore have to turn to experimental sensitization. The first investigators in this field observed that unless the material was applied to the epidermis they did not get eczematous sensitization. Sulzberger<sup>4</sup> was unable to sensitize guinea pigs to neoarsphenamine when the allergen was administered intramuscularly, intraperitoneally, intrapulmonally, intratesticularly or intracardially. The same pigs were subsequently sensitizable by intradermal injection of neoarsphenamine. Straus,<sup>5</sup> working with newborn infants, was unable to get sensitizations<sup>6</sup> by subcutaneous injection or by feeding of *Rhus* extract, whereas he easily succeeded (73 per cent of 48 infants) when the substance was applied to the skin. Simon,<sup>7</sup> in working with guinea pigs, observed that a good eczematous allergen, such as poison ivy, would not yield eczematous sensitization if it was injected intramuscularly, intravenously or intraperitoneally. In the older literature there were some reports on the successful development of eczematous sensitization when the allergen was given extraepidermally, but in none of these cases were any special precautions taken to avoid cutaneous contamination. The first experiments which employed careful technic and yet succeeded in producing eczematous sensitization by an extraepidermal route were those of Landsteiner and Chase.<sup>8</sup> These investigators observed that if they injected picryl chloride intraperitoneally they would occasionally get an eczematous sensitization but that the results were not constant and the sensitizations which did develop were of low intensity. If

4. Sulzberger, M. B.: Arsphenamine Hypersensitivity in Guinea-Pigs: II. Experiments Demonstrating the Role of the Skin, Both as Originator and as Site of the Hypersensitivity, *Arch. Dermat. & Syph.* **22**:839 (Nov.) 1930.

5. Straus, H. W.: Experimental Study of the Etiology of Dermatitis Venenata, *J. Allergy* **5**:568, 1934.

6. He did get sensitization in 1 case out of 10 cases in which the ivy extract was given by subcutaneous injection, but, as he states, it is difficult to be certain that the skin was not contaminated. It must be remembered that extraordinarily minute amounts will suffice to yield eczematous sensitization, particularly if one is working with concentrated material. My colleagues and I have found that in experiments in which we were endeavoring to avoid cutaneous contamination, when we used 2,4 dinitrochlorobenzene, we would usually think we had been successful, whereas, when we worked with paranitrosodimethylaniline we would usually be aware of contamination. The difference between the substances is, of course, that paranitrosodimethylaniline is a highly colored material and minute traces are easily visible, whereas 2,4 dinitrochlorobenzene is colorless. To offset this inherent difficulty with solutions of 2,4 dinitrochlorobenzene, in experiments of this character we now add a dye to the solution.

7. Simon, F. A.: Observations on Poison Ivy Hypersensitivity in Guinea Pigs, *J. Immunol.* **30**:275, 1936.

8. Landsteiner, K., and Chase, M. W.: Studies on the Sensitization of Animals with Simple Chemical Compounds: VII. Skin Sensitization by Intraperitoneal Injections, *J. Exper. Med.* **71**:237, 1940.

they concomitantly injected tubercle bacilli they consistently caused sensitizations of high intensity. They concluded: "It follows that although skin sensitization of this type is most easily obtained by dermal application this route of administration is no necessary condition for such sensitivity." The word "type" refers to "contact dermatitis type," the expression which the authors used in the sentence previous to the one quoted here. Gell<sup>9</sup> observed that animals would experience cutaneous sensitization to tetryl (N-methyl-*ar*,*N*-tetrannitroaniline) from subcutaneously implanted pellets made of tetryl. In fact, he achieved better sensitizations with this method than with intradermal injections. Sulzberger, Baer and Kanof<sup>10</sup> have noted that BAL (2,3 dimercaptopropanol) would yield sensitizations when applied to the skin by various technics and also when injected intramuscularly. The authors expressed the belief that the sensitization developed is not of the classic eczematous type, but the arguments which they adduce for this contention do not to me seem particularly convincing. In neither Gell's work nor in the work of Sulzberger and his associates were any particular precautions taken to avoid cutaneous contamination. It would thus appear that the easiest route by which eczematous sensitization can be achieved is by application of the material to the epidermis, but that does not mean that this is an essential route.<sup>11</sup> Why the application of the allergen to the epidermocutis should be better for the production of eczematous sensitization than the giving of the material by other routes can only be surmised, but, in my opinion, it is correlatable with the macrophage content of the tissue of conjugation and with the physical nature of the conjugate (soluble or not). These points will be discussed subsequently in the article.

#### WHAT HAPPENS TO THE ALLERGEN AT THE SITE OF APPLICATION?

In the naturally developing eczematous sensitization the material is applied to the epidermocutis, and consequently we are interested in

9. Gell, P. G. H.: Sensitization to "Tetryl," Brit. J. Exper. Path. 25:174, 1944.

10. Sulzberger, M. B.; Baer, R. L., and Kanof, A.: Clinical Uses of 2,3-Dimercaptopropanol (BAL): V. Skin Sensitization to BAL, J. Clin. Investigation 25: 488, 1946.

11. Actually, the term "epidermis" in this connection is not strictly correct inasmuch as eczematous sensitizations are achieved just as well by intradermal injections, which, as is well known, are not intraepidermal. Consequently, whether it is the epidermis or the cutis or both which participate in the reaction is unknown. In this article the terms "epidermocutis" and "epidermocutaneous" will be used to indicate that from the point of view of eczematous sensitization the epidermis or the cutis or the junction of the two is regarded as an immunologic unit and that the two are not, in the present state of knowledge, immunologically dissociable.

what happens to the allergen at this site. There would seem to be four theoretic possibilities: (1) that the allergen stays in situ, (2) that the allergen disseminates through or over the epidermis, (3) that the allergen is absorbed as such or (4) that the allergen reacts locally and a new substance is absorbed. Considering first the possibility that the allergen stays in situ, this implies that the sensitization is manufactured in the epidermocutis and that antibodies or some equivalent sensitizing materials are manufactured locally. At the termination of the incubation period then, these antibodies well over, so to speak, and by some means get to all the epidermocutis cells, so that the entire integument participates in the sensitivity. This moment is often indicated by a flare-up at the site of application of the allergen. This hypothesis is refuted by the work of Landsteiner and Chase<sup>12</sup> and of Simon,<sup>7</sup> who have shown that the site of application of the antigen in the case of poison ivy can be extirpated any time after the twelfth or twenty-fourth hour, respectively, and that the development of eczematous sensitization proceeds unhampered. Obviously, unless sensitization was already present at the time of extirpation it could not become generalized from excised skin. That the organism is not sensitive at this time is easily demonstrated by cutaneous tests, reactions to which are, as a rule, not positive until the sixth day, rarely earlier but not in any case at the twenty-fourth hour. The second possibility is that the allergen traverses the surface of the epidermis or disseminates through the epidermis via the prickle cell bridges or that it dissolves in a lipoidal material in the epidermis, thereby reaching the individual epidermocutis cells and by its presence causing them to develop the specific alteration in reactivity. While this is a theoretic possibility, it seems to be irreconcilable with two experimental facts. First, Landsteiner and Chase<sup>12</sup> and Schnitzer<sup>13</sup> have shown that if the allergen is applied to a cutaneous island which is made so as to sever completely all epidermocutaneous connections the generalization of the sensitization is not interfered with. Furthermore, Schnitzer<sup>13b</sup> has shown that a certain minimal concentration per unit of cutaneous area is required in order to induce eczematous sensitization and that if the simple allergen were distributed as previously mentioned there would be no need for this requirement. The third possibility, that the simple allergen is absorbed,<sup>14</sup> while it cannot be said to be completely disproved, is, in my opinion, extremely

12. Landsteiner, K., and Chase, M. W.: Studies on the Sensitization of Animals with Simple Chemical Compounds: VI. Experiments on the Sensitization of Guinea Pigs to Poison Ivy, *J. Exper. Med.* **69**:767, 1939.

13. (a) Schnitzer, A.: Untersuchungen über den Ausbreitungsmechanismus der ekzematösen Sensibilisierung, *Dermatologica* **83**:70, 1941; (b) Beitrag zur Frage des Mechanismus der Sensibilisierung, *ibid.* **85**:339, 1942.

14. By "absorbed" I mean that the allergen in its original form gets to the site where the hypersensitive state is induced.

of the lymphatics in the generalization of sensitization, certainly exclude the hypothesis that the generalized sensitivity is achieved because the allergen dissolves in and spreads through an epidermal lipoidal substance (Straus and Coca<sup>17</sup>), or that the allergen or the antibody disseminates by passing intraepidermally from prickle cell to prickle cell (Schreiber and Müller<sup>18</sup>). I believe that the compound allergen is probably absorbed primarily via the lymphatic channels but that other routes are also possible.

#### SITE OF THE DEVELOPMENT OF HYPERSENSITIVITY

Unfortunately, there is practically nothing known concerning the site of the development of hypersensitivity in the case of the eczematous sensitization. All that is known is that some time, usually six to nine days after the application of the sensitizing agent, the entire epidermis, as a rule, becomes sensitive. Just where or how this alteration in sensitivity is effected is not known. It can be stated, on the basis of the work previously referred to, that this alteration does not take place in the epidermis. From the evidence that a likely route of the absorption from the skin is via the lymphatic channels, it would appear that at least some of the material goes to the regional lymph node. This would be a reasonable site for the manufacture of sensitivity inasmuch as it is fairly well established in other types of immune reactions that antibodies are manufactured in the regional node (Ehrich and Harris<sup>19</sup>).<sup>20</sup>

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17. Straus, H. W., and Coca, A. F.: Studies in Experimental Hypersensitivity in the Rhesus Monkey: III. On the Manner of Development of the Hypersensitivity in Contact Dermatitis, *J. Immunol.* **33**:215, 1937.

18. Schreiber, W., and Müller, W.: Grundlegender Versuch zur Klärung der Frage, auf welchem Wege sich die Sensibilisierung in der Epidermis ausbreitet, *Dermat. Wchnschr.* **107**:1393, 1938.

19. Ehrich, W. E., and Harris, T. N.: The Formation of Antibodies in the Popliteal Lymph Node in Rabbits, *J. Exper. Med.* **76**:335, 1942.

20. There is much dispute in modern immunologic literature as to the relative role of the lymphocytes, macrophages and plasma cells in the formation of antibodies. As an amateur in this field, I can but hazard a guess, and that is that all three play a role, the relative importance in a given case being determined by the nature of the antigen. Literature on the role of the lymphocytes has been previously cited. Mention should also be made of the work of A. White and T. F. Dougherty (The Role of Lymphocytes in Normal and Immune Globulin Production, and the Mode of Release of Globulin from Lymphocytes, *Ann. New York Acad. Sc.* **46**:859, 1946). The role of macrophages has been treated by F. R. Sabin (Cellular Reaction to a Dye Protein with a Concept of the Mechanism of Antibody Formation, *J. Exper. Med.* **70**:67, 1939), and on the role of the plasma cells by M. Bjørneboe, H. Gormsen and F. Lundquist (Further Experimental Studies in the Role of Plasma Cells as Antibody Producers, *J. Immunol.* **55**: 121, 1947).

for X and Y. In other words, the skin from the sensitized person did not react in its new environment, whereas the skin from the non-sensitive person reacted in its new environment. Haxthausen interpreted this as showing that the sensitivity could not reside in the epidermis or it would be carried along with it, which it was not, and that there must be some humoral influences at work which caused the nonsensitive skin of B and Y to react in their new environment of A and X. The second experiment consisted of sensitizing a guinea pig and then connecting it by abdominal parabiosis to a normal pig. It was observed that the second pig also became sensitive. He interpreted this as corroborating the conclusion drawn from his previous experiment that there must be humoral influences at work which carry the sensitization. I believe that these experiments of Haxthausen's offer strong inferential evidence for the existence of some sort of humoral agency which is capable of transferring eczematous sensitization. These experiments do not shed any light on the question whether this humoral agency exists free in the tissue fluids or is carried intracellularly, as by lymphocytes.

#### SHOCK TISSUE AND THE SITE OF THE REACTION

The evidence favors the view that the epidermocutis is the shock tissue. The reasons for this belief are that clinical manifestations seem to be confined to the epidermocutis, and rarely do other tissues participate. For example, persons who are sensitive to poison ivy can, as a rule, chew the leaves with impunity. Jadassohn<sup>25</sup> has reported cases of epidermal sensitivity to iodoform in which the iodoform could be inserted intravaginally or into an ulceration and in neither case cause any reaction provided that it was applied carefully so as not to let any iodoform come into contact with the epidermis. Whether the manifestations of sensitization are as strictly limited to the epidermocutis in eczematous sensitization brought about by the extraepidermal introduction of the allergen is unknown.

#### SOME SPECULATIONS AS TO THE MEANING OF THE IMMUNOLOGIC FACTS

So far I have given some immunologic facts known about eczematous sensitization. It now remains to be seen whether these facts can be welded into a consistent whole. Obviously, any theory in the present state of knowledge is destined to have but a short life; however, its justification is that it may serve to point the way for further research. There are two points about eczematous sensitization which especially

25. Jadassohn, J.: A Contribution to the Study of Dermatoses Produced by Drugs, in Selected Essays and Monographs, London, New Sydenham Soc., 1900, no. 170, p. 207.

require elucidation. These are: (1) Why is the application of the allergen to the epidermocutis a superior route for the engendering of the sensitization and (2) what is the nature of the antibody in the sensitization and wherein does it differ from other more easily demonstrable antibodies?

In regard to the reason that application to the epidermocutis is a superior route, Sabin<sup>26</sup> has shown by direct evidence from the injection of an antigenic dye that the true cutis is distinctly richer in macrophages than is the subcutis, and, so far as I can gather, it is also richer than muscle. I have already referred to the fact that Landsteiner and Chase got no sensitizations or poor ones when they introduced picryl chloride intraperitoneally but good sensitizations when they concomitantly introduced tubercle bacilli. While a final opinion cannot be expressed, it seems probable that the adjuvant effect was achieved for the reason that the authors state: "In a general way, more rapid mobilization and modified activity of macrophages under the influence of tubercle bacilli—there is even greater phagocytic capacity for inert particulate matter—have been taken to be responsible for the effects mentioned." I therefore believe that the allergen has to be deposited in an area relatively rich in macrophages in order to effect an eczematous sensitization and that this is not the case when the material is given subcutaneously or intramuscularly. This, however, would not explain the failure when the allergen is given intraperitoneally or intravascularly. Here I believe that a different explanation has to be invoked. Landsteiner and Chase<sup>26</sup> failed to get cutaneous sensitization when they injected conjugates made with picryl chloride and either horse or guinea pig serum, but they succeeded<sup>27</sup> when they used conjugates made with picryl chloride and the stromas of guinea pig erythrocytes. What is the difference between these two conjugates? I believe that the essential difference is that the first is soluble and the second is not. Dr. Elmer L. Becker and I, in some unpublished observations (as yet on a preliminary scale), have succeeded in getting cutaneous sensitization to 2,4 dinitrochlorobenzene in the guinea pig by using either cutaneous or renal conjugates made in vitro with 2,4 dinitrofluorobenzene. The material was injected intraperitoneally and contained both soluble and insoluble fractions. It is certainly conceivable that the body handles particulate material and antigens differently. If this assumption is correct, then, of course, the failure to get eczematous sensitization with intravenous injection is explained. With intraperitoneal injection the situation is

26. Landsteiner, K., and Chase, M. W.: Studies on the Sensitization of Animals with Simple Chemical Compounds: IV. Anaphylaxis Induced by Picryl Chloride and 2,4 Dinitrochlorobenzene, *J. Exper. Med.* **66**:337, 1937.

27. Landsteiner, K., and Chase, M. W.: Studies on the Sensitization of Animals with Simple Chemical Compounds: IX. Skin Sensitization Induced by Injection of Conjugates, *J. Exper. Med.* **73**:431, 1941.

somewhat more complicated, as there probably are both soluble and insoluble conjugates formed, so that the material by itself yields a poor or not any sensitization. When an adjuvant which yields a good macrophage response is used, this may serve two purposes: (1) as a source of cellular (insoluble) material for conjugation and (2) as a source of phagocytes to take up the conjugate. Actually, the macrophages may pick up the simple chemical directly, and the conjugation may be intracellular. In view of the fact that sensitizations can be achieved with conjugates made in vitro, this does not seem likely.

The second point needing clarification is the nature of the eczematous antibody. The salient feature of this antibody is that it apparently does not exist free in the circulation. This may be correlatable with the fact that the full antigen incorporates a part of the body's protein into its being. As a result, when the antibody is manufactured a portion of its specificity is directed against the protein which participated in its formation. Because of this protein specificity the antibody would attach to tissue containing this protein. It is further postulated that this attachment constitutes the state of being sensitized but that a reaction becomes manifest only when the allergen (probably as the simple chemical) comes along to complete the reaction. I believe that in order to get a reaction in a sensitized animal, the substance used in the test has to be able to unite with the tissues in a way that the sensitizer did. Dr. E. L. Becker, who collaborated with me on a modified form of this theory, and I observed that the application of conjugation. It is thus seen that sensitive animals do not react if the skin of pigs that were sensitized to 2,4 dinitrochlorobenzene failed to cause reactions (unpublished). Further, animals that are sensitized to 2,4 dinitrochlorobenzene will not react to m-dinitrobenzene, which is presumably the part of the 2,4 dinitrochlorobenzene molecule left after conjugation. It is thus seen that sensitive animals do not react if the simple allergen is already conjugated or if it has been modified so that it can no longer conjugate.

#### CONCLUSION

The eczematous sensitization is brought about by the interaction of chemical compounds having the ability to form protein conjugates with certain of the body constituents. Ordinarily these protein conjugates are formed in the epidermocutis, but it is not believed that this is an essential requirement. The essential requirement is that these conjugates be formed in an area that is rich in macrophages. It is further believed that the conjugate must be of a relatively insoluble character. As a result of stimulation by such an antigen, an antibody is formed that has a cellular affinity, and this constitutes the state of being eczematously sensitized. An eczematous reaction, however, appears only when the simple chemical is brought into contact with the appropriate tissue.

## NEUROSYPHILIS

Treatment Using Penicillin Alone and in Combination with Oxophenarsine Hydrochloride and with Bismuth

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ROUTINE examination of spinal fluids of all syphilitic patients admitted to the New Mexico Intensive Treatment Center has been a valuable and productive procedure. The Center opened its doors on Feb. 7, 1944, and during its first two years and three months of operation, a total of 1,722 patients was admitted for intensive treatment of syphilis. Positive reactions of the spinal fluid were discovered in 259 patients (14.5 per cent). The large majority of these patients had never had examinations of spinal fluid before, although many of them had received varying amounts of irregular routine antisyphilitic therapy.

The present report deals with the results which were obtained with penicillin in the treatment of 171 patients, all followed up for periods from three to eighteen months. This number of patients represents 74.0 per cent of the total number who were treated for neurosyphilis with penicillin more than three months before this report and thus were eligible for follow-up examination.

A decision was made to use penicillin in treating these patients as a result of favorable reports in the literature. The initial observations of the Penicillin Panel of the Subcommittee on Venereal Diseases, National Research Council,<sup>1</sup> were encouraging. Follow-up examinations of spinal fluid in 107 patients with neurosyphilis that were studied by the panel showed improvement in 78 patients (slight in 43 and definite in 35), the commonest change being a reduction in the number of cells and in total protein. Symptomatic improvement was noted by such objective means as change in handwriting, encephalographic changes and the disappearance of ptosis and of headache associated with meningitis.

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Statistical data prepared by Mary B. Wicker.

1. Stokes, J. H.; Sternberg, T. H.; Schwartz, W. H.; Mahoney, J. F.; Moore, J. E., and Wood, W. B., Jr.: The Action of Penicillin in Late Syphilis Including Neurosyphilis, Benign Late Syphilis and Late Congenital Syphilis: Preliminary Report, J. A. M. A. 126:73-79 (Sept. 9) 1944.

Subsequent reports have continued this optimistic tone to a greater or lesser degree. Gammon and his associates<sup>2</sup> confirmed the beneficial effect of penicillin on the spinal fluid and noted that improvement began a few days after treatment with penicillin was started and reached a maximum in four months. Better results were obtained with higher dosage than with lower dosage, and best results were obtained with the higher dosage divided into two courses. The experience of Rose and his associates<sup>3</sup> in the treatment of patients with symptomatic neurosyphilis emphasized an immediate increase in cells and in total protein together with a temporary intensification of symptoms. They considered this phenomenon to be a Herxheimer reaction, since it occurred only in previously untreated patients. Subsequent reduction in cells and in protein to normal levels followed by a decrease in the intensity of the Wassermann reaction was likewise noted. Clinical results in 70 patients, followed up from four to twelve months after therapy, were tabulated as 28 patients "improved," 37 "no change" and 5 "worse," with the greatest improvement in patients with dementia paralytica.

Callaway and his associates<sup>4</sup> reported a "favorable therapeutic trend" in the condition of 100 patients with active syphilis of the central nervous system, each treated with a total of 4,000,000 units of penicillin over a ten day period. Sixty per cent of this series of patients showed clinical improvement associated with definite improvement in their spinal fluid, 31 per cent clinical improvement alone, 4 per cent improvement in spinal fluid unassociated with clinical change and 5 per cent clinical deterioration with no improvement or progression in spinal fluid. After therapy negative Wassermann reactions of the spinal fluid developed in 8 per cent of the patients. O'Leary<sup>5</sup> has also noted the prompt improvement in spinal fluids with both objective and subjective clinical improvement. Patients who had meningeal neurosyphilis were most benefited clinically and serologically, while patients who had parenchymatous neurosyphilis were helped only slightly if at all. Peni-

2. Gammon, G. D.; Stokes, J. H.; Beerman, H.; Ingraham, N. R., Jr.; Lentz, J. W.; Horgan, H. G.; Steele, W., and Rose, E. K.: Penicillin in Neurosyphilis: Effect on Blood and Spinal Fluid, *J. A. M. A.* **128**: 653-654 (June 30) 1945.

3. Rose, A. S.: Penicillin Treatment of Neurosyphilis, *Connecticut M. J.* **9**: 522-525 (July) 1945. Rose, A. S.; Travett, L. D.; Hindle, J. A.; Prout, C., and Solomon, H. C.: Penicillin Treatment of Neurosyphilis: A Preliminary Report of Seventy Cases Followed from Four to Twelve Months, *Am. J. Syph., Gonor. & Ven. Dis.* **29**: 487-493 (Sept.) 1945.

4. Callaway, J. L.; Noojin, R. O.; Flower, A. H., Jr.; Kuhn, B. H., and Riley, K. A.: The Use of Penicillin in the Treatment of Syphilis of the Central Nervous System, *Am. J. Syph., Gonor. & Ven. Dis.* **30**: 110-124 (March) 1946.

5. O'Leary, P. A.; Brunsting, L. A., and Ockuly, O.: Penicillin in the Treatment of Neurosyphilis, *J. A. M. A.* **130**: 698-700 (March 16) 1946.

cillin given in combination with fever therapy, either with malaria or by means of a fever machine, did not improve the clinical results noted from treatment with fever alone.

A recent thorough evaluation by Stokes and Steiger<sup>6</sup> of results in 283 patients with neurosyphilis who were treated with penicillin at the University of Pennsylvania has confirmed many of the earlier observations. Definite improvement in spinal fluid occurred in 74 per cent of the patients, and normal or near normal spinal fluids were attained in 36 per cent without regard to diagnosis. "Surprisingly little difference" was noted in the response to low dosage schedules compared with response to high dosage schedules. A comparison with older methods, including chemotherapy and fever therapy, indicates that in asymptomatic neurosyphilis treatment with penicillin ranks far above other methods in the degree of improvement, in spinal fluid, but malarial therapy still appears to be better in the production of clinical improvement. All the authors cited concur in the necessity for further observation for at least several more years before conclusive evaluation of the action of penicillin in treatment of patients with neurosyphilis can be accomplished.

#### MATERIAL

The 171 cases of neurosyphilis in this study were distributed as follows according to diagnosis:

Diagnosis	Number of Cases	Percentage
Asymptomatic neurosyphilis.....	125	73.1
Meningovascular syphilis.....	9	5.3
Tabes dorsalis.....	11	6.4
Dementia paralytica.....	20	11.7
Optic atrophy.....	6	3.5

The large majority of patients (73.1 per cent) were entirely asymptomatic, and the remaining patients had relatively mild and early manifestations. As a matter of policy, persons with symptomatic, advanced forms of the disease were not admitted to the Center for treatment. Accordingly, this study may be considered as representing an evaluation of results in the treatment of patients with asymptomatic neurosyphilis and of a small number with the disease in the mild early symptomatic phase. The percentage of male patients was 62.0 and of female patients 38.0. In this series there were 60.2 per cent native Spanish-speaking white persons, 33.3 per cent English-speaking white persons, 1.2 per cent Negroes and 5.3 per cent Indians. There were 11.1 per cent under 20 years of age, 47.4 per cent between 20 and 40 years of age and 41.5 per cent over 40 years of age.

6. Stokes, J. H., and Steiger, H. P.: Penicillin in Neurosyphilis, *J. A. M. A.* **131**:1-7 (May 4) 1946.

Penicillin alone was used in the treatment of 86 patients (50.3 per cent). The rest of the patients were divided into two groups, each receiving one of two forms of combined penicillin, oxophenarsine hydrochloride with penicillin and bismuth compound with penicillin. The schedules are referred to as the "8-6-3" schedule (40 patients, 23.4 per cent) and the "5-12-3" schedule (45 patients, 26.3 per cent).

The dosage schedule for penicillin alone is 40,000 units administered intramuscularly every three hours for sixty consecutive doses, making a total of 2,400,000 units. This schedule has been used widely for the treatment of early syphilis, especially by the Army and the Navy.

The "8-6-3" schedule, administered during an eight day period, comprises eight daily injections of oxophenarsine hydrochloride (0.06 Gm. for adults weighing more than 120 pounds [54 Kg.] and proportionately less for smaller patients, three injections of bismuth subsalicylate on the first, fifth and eighth days, and penicillin in doses of 10,000 units every three hours for sixty injections, making a total of 600,000 units.

Following the recommendation of the United States Public Health Service that schedule "8-6-3" be discontinued, a modification was employed which is known as the "5-12-3" schedule. During a nine day period, five injections of oxophenarsine hydrochloride are given on the first, third, fifth, seventh and ninth days. Three injections of bismuth subsalicylate, 200 mg. each, are given on the first, fifth and ninth days, and seventy-two injections of 16,667 units of penicillin every three hours are given for a total of 1,200,000 units.

The aforementioned three routines have been used at the Center for the treatment of patients with early or latent syphilis. The employment of these routines in the treatment of asymptomatic neurosyphilis was justified, my colleagues and I felt, by the initial reports of successful therapy with penicillin in neurosyphilis and also on account of the lack of adequate facilities for the administration of fever therapy in the state of New Mexico. Therapy combining penicillin, arsenic and bismuth did not appear to have any justifiable contraindication. The increased therapeutic effectiveness of combining arsenic and bismuth with penicillin has been noted in early syphilis.<sup>7</sup> We felt that the

7. (a) Moore, J. E.; Mahoney, J. E.; Schwartz, W.; Sternberg, T., and Wood, W. B.: The Treatment of Early Syphilis with Penicillin, *J. A. M. A.* **126**:67-73 (Sept. 9) 1944. (b) Schoch, A. G., and Alexander, L. J.: Treatment of Early Syphilis with Penicillin, *ibid.* **130**:696-698 (March 16) 1946. (c) Leavitt, H. M.: The Rapid Treatment of Syphilis: Comparison of Results Using Five Treatment Methods, *Am. J. Syph., Gonor. & Ven. Dis.*, **31**:27-40 (Jan.) 1947. (d) Eagle, H.; Magnuson, H. J., and Fleischman, R.: The Synergistic Action of Penicillin and Mapharsen (Oxophenarsine Hydrochloride) in the Treatment of Experimental Syphilis. *J. Ven. Dis. Inform.* **27**:3-9 (Jan.) 1946.

comparison of results of combined therapy with the results of therapy with penicillin alone presented an interesting problem worthy of investigation.

All patients with neurosyphilis were instructed to report for examinations of spinal fluid every three months until told not to do so any more. These patients were also instructed to report for monthly blood tests so that serologic changes could be observed. With few exceptions patients preferred to return to the Center for follow-up examination of spinal fluid, and almost all specimens were sent to the New Mexico State Public Health Laboratory for testing. These circumstances have provided a uniform series of follow-up laboratory reports furnishing the following information: Kolmer's complement fixation test in five dilutions, cell count, colloidal mastic test, Pandy's protein test and quantitative levels of total protein. We have successfully followed up 74.0 per cent of eligible cases for at least three months and most of these for over nine months.

#### SYMPTOMATIC RESULTS

Evaluation of clinical improvement has not been attempted in this study. Almost all patients (73.1 per cent) were entirely asymptomatic when therapy was initiated, and the remaining patients had symptoms of relatively low intensity. A feeling of general well-being was the rule when patients returned for follow-up examinations. The significance of this type of symptomatic improvement is difficult to determine, since penicillin undoubtedly exerts a beneficial, although perhaps temporary, effect on coincidental sinusitis, bronchitis, arthritis and other ailments associated with low grade infections, in addition to any amelioration of the symptoms of neurosyphilis. We have had no standards for measuring this symptomatic improvement in the neurosyphilis which we have encountered at the Center. Therefore this study will confine itself to objective changes noted in the blood and spinal fluid. It should be noted, however, that several striking examples of clinical deterioration have been observed along with simultaneous improvement in spinal fluid.

#### STANDARDS FOR EVALUATION OF RESULTS

The results of therapy were studied at three month intervals following treatment. Most patients had varying amounts of irregular routine antisyphilitic therapy before admission to the Center, but none had received fever therapy during the year preceding admission. None of the patients had received any form of rapid treatment for syphilis during the six month period preceding treatment here.

One of the objectives of this study is the demonstration of the effect of a single course of therapy in neurosyphilis. Accordingly,

we have studied the changes in spinal fluid following a single course of treatment for each of the 171 patients. To 35 patients (20.5 per cent) a second course of therapy, not usually the same as the first course, was given because of the appearance, persistence or progression of abnormal laboratory or clinical findings. The more severe the evidence observed, the earlier was retreatment instituted. Results of the second course of therapy have been studied separately.

The following terms were used in comparing follow-up observations of spinal fluid with the original observations preceding treatment: (1) worse, (2) no change, (3) slight improvement (return of cell count or colloidal mastic reaction to normal or clearing in one tube of the complement fixation test), (4) moderate improvement (clearing of two tubes of the complement fixation test or clearing of one tube of the complement fixation test plus return of cell count, colloidal mastic or total protein to normal levels), (5) much improvement (clearing of three tubes of the complement fixation test plus return of cell count, colloidal mastic or total protein to normal levels) and (6) negative (normal results for all tests, a cell count under 10 and levels of total protein under 40 mg. per hundred cubic centimeters).

Another method of demonstrating changes in spinal fluid is classification by groups. This classification, separating spinal fluids into three grades of pathologic changes, has been shown to have some significance in the evaluation of the extent of neurologic damage and the probable outcome in cases of asymptomatic neurosyphilis.

Group I. Fluids with elevated cell count and/or changes in protein; other aspects normal

Group II. Fluids with changes of moderate intensity in between groups 1 and 3

Group III. Fluids with maximal changes in complement fixation and in colloidal mastic tests (paretic formula)

A third method of evaluating changes in spinal fluid is the classification of each specimen report into "active" and "inactive" groups. An "active" fluid usually connotes a tendency toward progression of the pathologic process and inflammation of meningeal structures. An "inactive" fluid, on the other hand, suggests a quiescent or healing type of neurosyphilis, demonstrating response to therapy and a more favorable prognosis. An elevated cell count (over 10 cells per cubic centimeter) is the usually accepted standard for activity. We considered all levels of total protein over 40 mg. per hundred cubic centimeters of fluid and definitely positive reactions to Pandy's protein test as additional signs of activity. Previous reports have stressed the prompt reduction of activity in neurosyphilis in patients treated with penicillin. We have separated all reports on spinal fluid into active and inactive categories to determine to what degree our own experience bears out these reports.

Regular monthly follow-up blood tests have been studied for all of these patients in order to determine to what extent improvement in the serologic titer parallels changes in the spinal fluid.

#### RESULTS OF THERAPY

The results of therapy for the 171 patients in this study are presented in tables 1, 2 and 3. For 35 patients who received more than

TABLE 1.—*Changes at Last Examination of Spinal Fluid Following a Single Course of Therapy*

State of Spinal Fluid	Methods of Treatment			All Methods
	Penicillin	8-6-3	5-12-3	
Worse.....	5	6	2	13
Unchanged.....	6	3	5	14
Slightly improved.....	16	3	5	24
Moderately improved.....	28	7	14	49
Much improved.....	13	8	7	28
Normal.....	18 (20.9%)	13 (32.5%)	12 (26.7%)	43 (25.1%)
Total cases.....	86	40	45	171

one course of treatment the results of the first course only are included. At the last follow-up examination of each of the 171 patients, 24 showed slight improvement, 49 showed moderate improvement, 28 showed much improvement and 43 (25.1 per cent) became entirely normal.

TABLE 2.—*Classification of Spinal Fluid by Groups Before Treatment and at Last Examination Following a Single Course of Therapy*

Method	Group	Number Before Treatment	Number After Treatment
Penicillin alone.....	Normal	0	18
	I	5	5
	II	62	59
	III	19	4
"8-6-3".....	Normal	0	13
	I	0	0
	II	29	25
	III	11	2
"5-12-3".....	Normal	0	12
	I	5	4
	II	28	27
	III	12	2
All methods.....	Normal	0	43
	I	10	9
	II	119	111
	III	42	8

In order to compare each of the three methods of treatment, the term "definite improvement" is used, meaning the total of cases which fall into the groups classified as "moderate improvement," "much improvement" and "entirely normal." Definite improvement was noted in 68.6 per cent of the patients treated by penicillin alone, 70.0 per

cent of the patients treated by the "8-6-3" schedule, and 73.3 per cent of those treated by the "5-12-3" schedule.

It was noted that 20.9 per cent of the patients treated with penicillin alone succeeded in achieving normal spinal fluid, compared with 32.5 per cent for the "8-6-3" schedule and 26.7 per cent for the "5-12-3" schedule.

Spinal fluid became worse in only 13 patients (7.6 per cent). One of these patients had optic atrophy, which rapidly progressed to blindness, seemingly in spite of therapy. The other patients in this small group showed only slight changes for the worse.

TABLE 3.—*Classification of Spinal Fluid by Activity Before Treatment and at Last Examination Following a Single Course of Therapy*

Method	Activity	Number Before Treatment	Number After Treatment
Penicillin alone.....	Normal.....	0	18
	Active.....	50	27
	Inactive.....	36	41
"8-6-3".....	Normal.....	0	13
	Active.....	28	11
	Inactive.....	12	16
"5-12-3".....	Normal.....	0	12
	Active.....	31	16
	Inactive.....	14	17
All methods.....	Normal.....	0	43
	Active.....	109	54
	Inactive.....	62	74
All methods (percentage) ..	Normal.....	0	25.1
	Active.....	63.7	31.6
	Inactive.....	36.3	43.3

Before therapy 10 patients were in group I, 119 in group II, and 42 in group III. At the last follow-up examination 43 patients were entirely normal, 9 were in group I, 111 in group II, and 8 in group III.

Before therapy the spinal fluid in 109 patients was classified as active and in 62 as inactive. At the last follow-up examination the spinal fluid was active in 54 patients, and in 117 it was inactive or entirely normal.

Thirty-five patients were treated with more than one course of therapy, and the results of the first course are included in the foregoing figures and in tables 1, 2 and 3. A separate analysis of changes in spinal fluid after the second course of therapy shows a tendency toward continued improvement. Three patients showed no change, 4 showed slight improvement, 4 showed moderate improvement and 2 became completely normal. The rest were not available for follow-up examination.

Examination of the blood at monthly intervals failed to show any considerable diminution in titer in almost all of the patients in this

of therapy with penicillin before resort to the severer fever therapy. Many patients suffering from neurosyphilis cannot undergo fever therapy because of debility, complicating constitutional disease, obesity or age. In penicillin we now have a promising form of therapy which can be administered safely and in repeated courses if necessary.

This study has stressed the immediate effect of a course of penicillin therapy with a total dosage of not more than 2,400,000 units. We have been successful in improving the spinal fluid of the large majority of patients treated. Evaluation of the effect of the second course of therapy on spinal fluid is inconclusive because of the small number of patients. Our figures suggest that the tendency toward clearing of the spinal fluid is continued by the second course, but the changes are mostly slight and moderate. The remarkable improvement noted in most patients after the first course of therapy is not seen. We cannot help feeling that, in some instances at least, retreatment has been premature, and that the continued improvement might well be due to the first course of therapy as much as to the second.

A check of the 43 patients whose spinal fluids were normal after a single course of penicillin therapy shows that before therapy 5 of these patients were in group I, 35 in group II, and only 3 in group III. This indicates a better prognosis for patients in groups I and II treated by penicillin and is in accord with the expected results of other forms of therapy, including therapy with arsenicals and fever. Thus, the speed of reversion to complete normality is to some extent a function of the degree of original abnormality.

We have not made an attempt to compare the results of therapy with penicillin with results of therapy with fever, since much more comprehensive study is necessary to shed light on this interesting problem. Follow-up evaluation of change in spinal fluid following malarial therapy cannot be accomplished effectively until two to five years have elapsed. Also, careful selection of comparable cases is needed, since it has been demonstrated that the response to therapy with penicillin in asymptomatic neurosyphilis and in meningovascular syphilis is much more favorable than the same therapy in parenchymatous forms of the disease.

We have not noted serious reactions in these patients as a result of therapy with penicillin. Nevertheless, one should be cautious in commencing treatment of a previously untreated patient, especially when meningeal involvement or cardiovascular damage is suspected, since Herxheimer reactions of serious import have been reported.

#### SUMMARY

One hundred and seventy-one patients with neurosyphilis, mostly asymptomatic, were treated with a single course of penicillin alone or with a course of penicillin combined with oxophenarsine hydrochloride

## SPOROTRICHOSIS

Report of a Case in Which Treatment with Iontophoresis Was Successful

LOREN W. SHAFFER, M.D.

AND

HERSCHEL S. ZACKHEIM, M.D.

DETROIT

THE FOLLOWING case of sporotrichosis is reported since it demonstrates the efficacy of iontophoresis with strong solution of iodine, U. S. P., and the failure of penicillin in the therapy for this disease. While sporotrichosis is usually responsive to treatment with potassium iodide administered orally, an occasional case is encountered in which the disease is resistant to this form of therapy or in which intolerance to large doses of potassium iodide administered by mouth exists.<sup>1</sup> The disease is not a rarity here, yet we have been able to find only 1 other case proved by culture which has been reported from Michigan.<sup>2</sup>

### REPORT OF A CASE

W. C., a 72 year old Negro, was first seen in the Dermatology Clinic of City of Detroit Receiving Hospital on March 9, 1945 for treatment of numerous nodular and suppurative lesions of the left hand, forearm and arm of three months' duration.

*Past History.*—The patient's past history was irrelevant. He was born in North Carolina and had resided continuously in Detroit since 1926.

*Present Illness.*—The patient cut his left thumb while working in a woodpile during the last week of December 1944. On Jan. 30, 1945 he was admitted to the surgical wards of City of Detroit Receiving Hospital presenting an ulcer at the base of the left thumb, cellulitis of the left hand and forearm, indurated lymphatic channels of the arm and moderate axillary lymphadenopathy. The cellulitis subsided on a regimen of hot magnesium sulfate wet dressings, and he was discharged after four days to be followed through the outpatient department. On February 6 several subcutaneous nodules were noted on the left forearm, and two weeks later ten nodules were counted.

*Examination.*—On March 9, when he was referred to the Department of Dermatology, the patient presented a series of twenty-six discrete subcutaneous

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From the Department of Dermatology and Syphilology, Wayne University College of Medicine and City of Detroit Receiving Hospital, Detroit.

1. Ray, L. F., and Rockwood, E. M.: Sporotrichosis: Report of a Case in Which It Was Resistant to Treatment, Arch. Dermat. & Syph. **46**:211 (Aug.) 1942. Loewe, G.: Sporotrichosis of the Cervical Area, J.A.M.A. **107**:1040 (Sept. 26) 1936.

2. Menagh, F. R.: Sporotrichosis: Report of a Case, Arch. Dermat & Syph. **38**:313 (Aug.) 1938.

solution and wrapped about the arm. Strips of pliable metal were then wound about the toweling spirally. Since the active ion, iodine, is an anion, the negative electrode was attached to the arm, and the large indifferent positive electrode, a moist pad, was placed on the back. For the first two weeks the entire arm was treated in one application, but thereafter separate applications were made to the hand, the forearm and the arm, as the patient was then able to tolerate a greater current to each region. The current was about 15 milliamperes for twenty minutes in the first week, but this was later gradually increased to about 35 milliamperes for thirty minutes to each of the three areas.

After two weeks of such treatment there was striking clinical improvement, although pus could be expressed from a few nodules and cultures were positive. After seven weeks only a few nodules remained, and no suppuration was evident. After eleven weeks all lesions had either been replaced by scar tissue or had healed, leaving only pigmentation, except for a small nonsuppurative nodule at the base of the thumb. Treatment was discontinued. However, two weeks later a few drops of pus were expressed from this remaining lesion, and cultures were again positive. After five days of iontophoretic treatment pustulation had ceased, and after another week of therapy there were no signs of activity. Therapy was then terminated. At no time had the patient received any other local or oral medication. He was last seen six months after termination of therapy and showed no signs of relapse.

*Intradermal Test.*—An intradermal test was performed five months after complete healing of all lesions with 0.1 cc. of a 1 to 1,000 dilution of a vaccine prepared from cultures obtained from the patient. After forty-eight hours an inflammatory nodule, measuring 25 mm. in diameter with central pustulation and surrounding erythema, was present. Similar intradermal injections in 5 control patients produced papules 3 to 5 mm. in diameter and were considered as having elicited no significant reaction.

#### STREPTOMYCIN

Serial dilutions of Sabouraud's 4 per cent dextrose broth containing concentrations of streptomycin as high as 256 units per cubic centimeter failed to inhibit the growth of *S. schenki* in inoculations. We therefore feel that streptomycin will be of no value in treating patients with sporotrichosis.

#### COMMENT

The time-consuming nature and technical difficulties of iontophoresis would not justify its use as the treatment of choice for sporotrichosis. In view of its proved efficacy, potassium iodide administered orally, either alone or in combination with roentgen ray therapy, should be routinely used. However, treatment with iontophoresis may prove to be of value in the occasional case in which the disease does not respond to oral iodides, or in which symptoms of intolerance to large oral doses of iodides may develop. We also feel that in view of the extensive involvement in this case the time required for complete healing of all lesions, thirteen weeks, compares favorably with that required with the usual methods of therapy. In view of the recent work of

## LUPUS ERYTHEMATOSUS TREATED WITH VASODILATORS AND COLLOIDAL GOLD SULFIDE

FREDERICK REHM SCHMIDT, M.D.  
CHICAGO

**T**HIS report deals with the results obtained in the treatment of lupus erythematosus with vasodilators and colloidal gold sulfide. Some interesting observations on the relationship of leukopenia, albuminuria and hypertension to the clinical condition of patients were noted.

Kuehnau<sup>1</sup> and Tarentelli<sup>2</sup> were among the early investigators to employ vasodilator therapy in lupus erythematosus. They used the amide of nicotinic acid and reported encouraging results. Recently I reported on the theory and practical use of vasodilators in the management of various dermatoses.<sup>3</sup> Rapid improvement was noted in erythema multiforme and in actinic eruptions. My conclusions were confirmed by Weisberg and Rosen.<sup>4</sup>

For many years I have entertained the idea that anoxia of tissue induced by spasm of the blood vessels prevents gold from reaching the unhealed active lesions of lupus erythematosus. This belief was substantiated by the experiments of Beinhauer, Jacob and Beebe,<sup>5</sup> who found that gold was present in quantities large enough to be demonstrated spectrographically in the healed lesions of lupus erythematosus in patients treated with gold sodium thiosulfate, while little if any of the metal was detected in active lesions. This fact probably accounts for the favorable response to treatment reported by Monash

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Read at the Sixty-Sixth Annual Meeting of the American Dermatological Association, Inc., June 13, 1946.

From the Northwestern University Medical School and the Outpatient Department of Grant Hospital.

Hille Laboratories, Chicago, supplied a large part of the colloidal gold sulfide used in these studies.

1. Kuehnau, W. W.: Treatment of Lupus Erythematosus with Nicotinic Acid Amide, *Klin. Wchnschr.* **18**:1117 (Aug. 19) 1939.
2. Tarentelli, E.: Clinical Observation on the Use of Nicotinic Acid in Dermatology, *Policlinico (sez. prat.)* **48**:61-64 (Jan. 13) 1941.
3. Schmidt, F. R.: Treatment of Dermatoses with Vasodilators, *Arch. Dermat. & Syph.* **52**:344-346 (Nov.-Dec.) 1945.
4. Weisberg, A., and Rosen, E.: Erythema Exudativum Multiforme, *Arch. Dermat. & Syph.* **53**:99-106 (Feb.) 1946.
5. Beinhauer, L. G.; Jacob, F. M., and Beebe, P. L.: Spectrographic Analysis of Gold in the Skin Following the Treatment of Lupus Erythematosus, *Arch. Dermat. & Syph.* **50**:315-319 (Nov.) 1944.

and Traub<sup>6</sup> when gold was deposited directly in the lesions by intra-cutaneous injections.

A form of gold compound was employed in this investigation that has proved nontoxic even when given in relatively large amounts. This is colloidal gold sulfide, a product containing 86 per cent metallic gold and 14 per cent sulfur in true colloidal form. Each cubic centimeter of the product contains 17.2 mg. of metallic gold. Gold sodium thiosulfate, on the other hand, contains on the average only 3.5 mg. of elemental gold per cubic centimeter of the product. This means that colloidal gold sulfide is much more potent than is indicated by its gold content, because colloids possess a far greater amount of surface energy and catalytic power than do the comparatively weaker crystalline gold salts.

An initial dose of 2 cc. of colloidal gold sulfide is recommended, regardless of whether the intramuscular or the intravenous route is chosen. This is increased to 3 and then to 4 cc. at intervals of four days, after which 5 cc. should be administered every five or six days.

Colloidal gold sulfide may be given not only by the intravenous and by the intramuscular route but also by mouth, an obvious advantage in treating children and persons whose occupation compels them to travel. The oral dosage is still far from being definite, because relatively little colloidal gold sulfide has been given orally. It is suggested that adults take 20 drops three times daily in water or milk after meals. This dosage supplies 150 mg. of metallic gold weekly. Children should take 1 drop three times daily for every 8 pounds (3.6 Kg.) of weight.

To increase the flow of blood to the skin by overcoming vasospasm, 1 tablet of 100 mg. of nicotinic acid is taken after each meal. An additional tablet should be taken fifteen minutes before injection of the gold compound. The amide nicotinic acid does not produce desired flushing of the skin. The dose of nicotinic acid is cut to 50 mg. if the feeling of warmth is uncomfortable. Smoking should be prohibited, because tobacco has an anoxemic effect, similar to the effect of epinephrine, and this tends to neutralize the vasodilating action of nicotinic acid. Exposure to cold and undue physical exertion should be avoided, for they, also, have a vasospastic effect and thus deprive the skin of oxygen.

Throughout the first two years of this study, a watchful eye was kept on the leukocyte count, the sedimentation rate of the erythrocytes, the urine, the blood pressure and particularly the skin for signs of pruritus or of dermatitis. This vigilance was somewhat relaxed after some three hundred and fifty injections had demonstrated that toxic effects from the use of colloidal gold sulfide did not occur.

6. Monash, S., and Traub, E. F.: Modification Therapy with Gold Compounds in Lupus Erythematosus: Preliminary Communication, Arch. Dermat. & Syph. 24:110-111 (July) 1931.

Fatigue is a common complaint of women of the childbearing age afflicted with this disease. Frequent rest periods of twenty minutes each during the day are advisable. Anemia due to iron deficiency must be combated with large doses of ferrous sulfate. Dermatologists are prone to overlook the patient's general condition, which is one reason for the ever increasing loss of patients to internists.

An icteric index was obtained in many patients, because Block, Buchanan and Freyberg<sup>7</sup> showed that gold was found in large amounts in the liver of animals receiving colloidal gold sulfide. This is in contrast to the results when a crystalline gold salt, such as gold sodium thiosulfate, was administered, in which case the kidneys contained the larger amounts of gold.

The fate of gold introduced into the blood stream is uncertain. Experiments indicate that colloidal gold is deposited in the liver where it is quickly taken up by the reticuloendothelial cells. This may be its fate in the skin. At any rate, it disappears rapidly from the blood, for concentrations of colloidal gold in the blood plasma are low a short time after intravenous administration of the gold compound.

Thirty patients were treated in this manner; 26 had the chronic discoid type of lupus erythematosus, while the remaining 4 were in the subacute phase. Tabulation of clinical results is omitted from this paper, chiefly because the varied response in individual patients is well known, a tendency to spontaneous involution in some and a tendency to recurrence in others.

A study of these patients reveals that clinical improvement under treatment with colloidal gold sulfide was noticeable in all but 5. Two of the 5 failures occurred in patients exhibiting the subacute type of lupus erythematosus. Four of the patients who improved with this management had previously failed to respond to injections of oxo-phenarsine hydrochloride, while the majority of the remainder had failed to respond to treatment with a bismuth compound or with gold sodium thiosulfate in varying amounts. The response to treatment bore no relationship to the duration of the disease or to the amount and degree of atrophy. Many of the patients with a history of having had the disease for more than ten years showed clinical arrest in a shorter time than did those who had had it for a relatively brief time. Relapse was observed in 9 patients when chrysotherapy was stopped and either a bismuth compound or liver was substituted.

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7. Block, W. D.; Buchanan, O. H., and Freyberg, R. H.: Metabolism Toxicity and Manner of Action of Gold Compounds in the Treatment of Arthritis: Comparative Study of Distribution and Excretion of Gold Following Intramuscular Injection of Five Different Gold Compounds, *J. Pharmacol. & Exper. Therap.* **73**:200-204 (Oct.) 1941.

## SUMMARY

This report deals with the therapeutic results obtained in 30 patients with lupus erythematosus, chiefly of the chronic discoid type, with the administration of nicotinic acid by mouth and of colloidal gold sulfide intravenously and intramuscularly.

Lasting clinical arrest in this capricious disease is apparently more quickly attained with the combined form of therapy outlined in this report than with former modalities of treatment.

Larger doses of gold than have previously been employed are recommended in the treatment of lupus erythematosus, since the most favorable results were observed in patients receiving relatively large amounts of gold.

The response to treatment appears to be correlated with the degree of peripheral flush induced by nicotinic acid.

These studies further demonstrated that the presence of severe leukopenia, hypertension or albuminuria in persons with lupus erythematosus is no contraindication to treatment with colloidal gold sulfide and vasodilators. It is interesting to note that no correlation could be determined or prognostic deductions made from the level of the white blood cell count, the sedimentation rate of the erythrocytes, the icteric index and the degree of activity of the disease.

No toxic reactions were observed.

122 South Michigan Avenue.

## DISCUSSION

DR. LAWRENCE G. BEINHAUER, Pittsburgh: Any therapeutic approach in the treatment of lupus erythematosus is always welcome in a disease in which the therapeutic response has not been uniformly satisfactory. We have been much interested in evaluating the failure of all the lesions of this disease to respond when subjected to gold therapy. We reported at a previous meeting of this association our experiences in determining, by spectrographic means, the distribution of gold in inactive (healed) lesions as well as in the normal skin of patients with this disease receiving gold therapy. We proved to our satisfaction that the presence of gold in the diseased tissues was associated with healing, but we have been unable to determine why gold was always present in the healed lesions and absent in the active lesions.

What mechanism or what barrier existed that prohibited gold from uniformly entering all the diseased tissue is only a matter of conjecture, and only future study will determine this point.

Dr. Schmidt advances the theory that local tissue anoxia, induced by the spasm of the blood vessels, is a reason that gold does not reach the unhealed or the active lesions in this disorder. He suggests the use of a vasodilator, namely, nicotinic acid, as a method of approach, requiring, however, that definite flushing or vasodilatation be present to allow the gold to reach the desired area. This point, we feel, can be approached by the spectrographic examination for gold in these tissues, which may offer substantiation of the theory which he has advanced.

It is interesting to note that the colloidal gold sulfide is nontoxic and can be utilized in relatively higher dosage with safety, and on that basis it warrants future

of the liver who had a dermatitis-herpetiformis-like eruption which was extremely pruritic. We all know that cinchophen is capable of producing various types of cutaneous disorders, and yet cinchophen is toxic to the liver.

There was another example of a severe pruritic eruption of many years' duration in a patient who had cirrhosis of the liver which was never diagnosed during life. The diagnosis was made at autopsy. Jaundice associated with inflammations and with neoplasms is very pruritic.

The two presentations that we have had at this meeting should stimulate us to do further research in the physiologic aspects of dermatology.

DR. E. WILLIAM ABRAMOWITZ, New York: We always welcome a new drug or a modification of an old drug to our armamentarium. Gold is gold, and any preparation of it is toxic. The introduction of a new compound of silver was always heralded as safe and claims were made that argyria was not to be feared. These claims failed to materialize.

The use of nicotinic acid in connection with the gold as a vasodilator may prove a valuable addition to the therapy of lupus erythematosus, especially the discoid type. In the Hollander method, with the use of quinine internally and tincture of iodine applied externally, the curative effect was attributed to the action of nascent iodine at the affected site. Perhaps it was not the iodine but the vascular dilatation that developed at the site of the iodine application that accounted for the good results sometimes obtained.

Dr. MacKee has used in some cases of gold-resistant lupus erythematosus of the discoid type mild local applications of solid carbon dioxide to impose vascular dilatation and to encourage increased deposits of the gold compound at the involved areas.

The cardiologists have noticed the favorable effect of nicotinic acid in cardiovascular disease.

I wish to describe a serious reaction from gold that receives only passing mention in the literature. A woman in the early fifties experienced a subacute disseminated type of lupus erythematosus for which she received six or seven injections of 100 mg. of gold sodium thiosulfate intravenously. There was no doubt about the effect of the gold on the cutaneous lesions, but a severe hemorrhagic colitis developed and the patient required hospitalization for two or three months. I was told that several other cases were encountered by gastroenterologists in patients who were being treated for rheumatoid arthritis with various gold preparations.

DR. SAMUEL AYRES JR., Los Angeles: I would like to ask one question. Doesn't the very fact that lupus erythematosus consists of erythematous lesions indicate the presence of vasodilatation in the lesions as they already exist?

DR. FREDERICK R. SCHMIDT, Chicago: I thank the gentlemen who discussed this paper. I certainly am not one to say that this treatment is a cure for this capricious disease, and I heartily subscribe to Dr. Oliver's remark that this modality of treatment has brought improvement in these cases in a shorter length of time than has the older form of treatment in a comparable series of cases, and that is all.

The expense of the treatment is not so great when one considers that this preparation contains 17.2 mg. of gold per cubic centimeter compared with 3.5 mg.

I heartily subscribe to what Dr. Abramowitz said about the toxicity of gold. I merely want to say that this colloidal gold preparation has been used for many years in the treatment of arthritis without any cases of toxicity being reported, so that it is nothing new.

## CLINICAL EVALUATION OF UNDECYLENIC ACID AS A FUNGICIDE

EMANUEL MUSKATBLIT, M.D.  
NEW YORK

DURING recent years there have appeared in the literature several reports concerning the fungicidal action of various fatty acids and their salts. The undecylenic acid was discovered to be most effective in laboratory and clinical experiments. Only clinical observations, however, are decisive in evaluating the usefulness of chemical substances in the treatment of fungous diseases of the skin. Laboratory tests *in vitro* are interesting but not convincing. Often chemicals which give striking results with fungous cultures in test tubes prove entirely useless when applied to human skin.

The observations herein reported were made during the period from October 1944 to January 1946 on patients of the New York University Skin Clinic who were suffering from fungous infections of the skin and nails. Ringworm of the scalp was not included in this investigation.

The diagnosis in all cases was established by microscopic examination of scrapings. Cultures were made only at the beginning of the treatment in order to identify, if possible, the species of fungus involved. Further laboratory controls were made only microscopically. Patients were asked to come to the clinic once a week or once in two weeks. Some, however, did not come regularly. These facts should be taken into consideration in estimating the duration of treatment necessary for a cure.

Two preparations known as "desenex ointment" and "desenex powder" were used. The ointment contains 5 per cent undecylenic acid and 20 per cent zinc undecylenate in a vanishing type base. The powder consists of 2 per cent undecylenic acid and 20 per cent zinc undecylenate in talc.<sup>1</sup> The patients were instructed to rub the ointment into the affected parts of the skin and then to dust with the powder. This procedure was repeated twice daily. The area was washed with soap and water once or twice daily. In cases of fungous

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From the Department of Dermatology and Syphilology of the New York University College of Medicine on the service of Dr. Frank C. Combes.

1. The preparations used in this investigation were supplied by the Research Department of Wallace and Tiernan Products, Inc., Belleville, N. J.

Four of the cured patients had three microscopic examinations showing absence of fungi, and in 2 of them some scaling and maceration persisted.

A microscopic examination showing freedom from fungi is especially significant if it is obtained after the treatment has been discontinued. In 6 out of 18 cured patients the microscopic examination showed freedom from fungi from two to five weeks after the treatment had been stopped. In all 18 cured patients there were no microscopic relapses. When the microscopic examination showed absence of fungi, it continued to do so if repeated a second and a third time.

TABLE 1.—*Clinical Form of Dermatomycosis, Laboratory Data and the Results of Treatment*

Diagnosis	Laboratory Results	Number of Cases	Results of Treatment		
			Cure	Doubtful	Failure
Dermatophytosis of feet	T. interdigitale .....	8	5	1	2
	T. purpureum .....	2	..	1	1
	E. inguinale .....	1	1	..	..
	Monilia (microscopically only) and T. interdigitale .....	1	..	..	1
	Microscopic evidence of ringworm type only .....	16	12	3	1
Total of dermatophytosis of feet		28	18	5	5
Dermatophytosis of hand	Microscopic evidence of ringworm type only .....	1	1	..	..
Generalized derma- tomycosis	T. purpureum and E. inguinale.....	1	1	..	..
Tinea cruris	Microscopic evidence of ringworm type only .....	1	1	..	..
Onychomycosis	Microscopic evidence of ringworm type only .....	2	1	1	..
Monilliasis	Microscopic evidence of ringworm and monilial types mixed.....	2	..	..	2
	Monilia albicans microscopically and in cultures .....	2	..	..	2
Pityriasis versicolor	Microscopic evidence only.....	6	4	..	2
Total of all cases.....		44	27	6	11

Table 2 shows the duration of treatment required for cure in patients with dermatophytosis of the feet. Since the patients were coming to the clinic at intervals of one to two weeks, the periods of time given in the table should be regarded as maximum. The actual cure could have taken place somewhat earlier than indicated.

This table shows that the patients in all cases except 1 were cured in two to seven weeks. The last patient was registered as cured after fourteen weeks of treatment only because he failed to come to the clinic for two months.

Cultures were successful in only 6 out of 18 cured patients. Trichophyton interdigitale was grown from 5 patients who were cured in four to seven weeks. Epidermophyton inguinale was obtained from 1 patient who was cured in two weeks.

## TINEA CRURIS

One case of tinea cruris was treated. Itching disappeared in a few days, and the patient was cured both clinically and microscopically in eleven days.

## GENERAL DERMATOMYCOSIS

The first patient with generalized dermatomycosis was a woman with involvement of the toes, thighs and buttocks. Fungi of ringworm type were observed microscopically in all affected parts. The itching disappeared on the second day after the beginning of the treatment. Three weeks later the skin was almost completely clear, and the scrapings were free from fungi. Two months later the patient informed the clinic by telephone that her skin was "perfectly normal." This patient was considered cured.

The second patient was a man with lesions on toes, soles, and buttocks. Some of his toe nails and finger nails were also affected. All these parts showed ringworm fungi on microscopic examination. Cultural observations were of unusual interest. The groin showed *S. inguinale*, the soles showed *T. purpureum* and the toes both with parasites together. Cultures from the buttocks and nails failed. Treatment was successful as far as the skin was concerned. Toes and groin were cured in four weeks and soles in six weeks. The lesions on the buttocks were more resistant and required three and one months of treatment. It is noteworthy that *T. purpureum*, a resinous species, was cultured from the toes and the soles. Both cleared clinically and were twice observed to be microscopically free from fungi.

## GENERAL REVIEW OF RINGWORM INFECTIONS OF GLABROUS SKIN

*Duration of the Disease.*—The duration of the disease has influence on the duration of treatment necessary for a cure. The history given by the patient is usually unreliable. The patient fails to notice the changes in the toe webs for a long time or he calls "ringworm" or "athlete's foot" a condition which was not of fungous causation. It can be pointed out, however, that 1 patient had a history of having had the infection for only one month requiring six weeks of treatment while other patients with histories of having had the infection up to fifteen years were cured in two weeks.

*Clinical Type of Lesions.*—The clinical type of the lesions, whether erythematous, squamous, intertriginous, fissured, vesicular or bullous, had no influence on the result of therapy. It should be noted also that there were no cases of the distinctly hyperkeratotic type, which is considered more resistant to treatment.

*Effect of Undecylenic Acid on Itching.*—The effect of undecylenic acid on itching was, in general, good. One patient stated that it disappeared on the second day after the beginning of the treatment.

## PITYRIASIS VERSICOLOR

Of 6 patients with pityriasis versicolor, 3 were cured both clinically and microscopically in from one to four weeks. The fourth case cleared clinically after two and one-half weeks of treatment. It was registered as cured although the patient did not come for a microscopic examination. The fifth patient was not cured after ten days of treatment as determined clinically and microscopically. The sixth case of pityriasis versicolor was unusually resistant. Repeated clinical and microscopic relapses were observed. The patient presented visible lesions and fungi were observed microscopically after four months of treatment.

None of the 44 patients with various fungous diseases who were treated with preparations containing undecylenic acid showed any objective or subjective evidence of cutaneous irritation due to this chemical substance. If one takes into consideration that some patients presented acute inflammatory vesicular and bullous lesions for which the old reliable fungicidal chemicals such as salicylic acid and sulfur were contraindicated because of the possibility of dermatitis venenata, the importance of the lack of evidence of cutaneous irritation becomes obvious.

## SUMMARY AND CONCLUSIONS

Two new preparations ("desenex"), an ointment containing 5 per cent undecylenic acid and 20 per cent zinc undecylenate and a powder containing 2 per cent of the same acid and 20 per cent of its zinc salt, were used for treatment of various fungous diseases of the skin, which were proved microscopically and, in part, culturally.

Forty-four patients who were treated with undecylenic acid presented the following clinical forms: dermatophytosis of the feet (28), of the hand (1), generalized (2), tinea cruris (1), onychomycosis (4), moniliasis (2) and pityriasis versicolor (6). The patient was considered cured when the skin became clinically normal and microscopically free from fungi. In some patients with slight remaining cutaneous changes a microscopic examination showing absence of fungi was considered sufficient proof that a cure had been achieved.

Of 32 patients with dermatophytosis of varied localization and tinea cruris, 22 (68.7 per cent) were cured, the results for 5 remained doubtful and in 5 the treatment failed. The cure required from eleven days to three and one-half months, the average time being thirty-five days. The duration of the disease and the clinical type of the lesions had no influence on the duration of the treatment necessary for cure. In some cases fungi could be observed microscopically several weeks and even three and one-half months after the beginning of the treatment. The number of positive cultures was too small for definite conclusions. It can be noted, however, that 5 of 8 patients with infection due to *Trichophyton interdigitale* were cured, as were 2 patients with infection

## EXTRAGENITAL CHANCRE OF THE EAR

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EAST BOSTON, MASS.

AND

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**E**XTRAGENITAL chancres may be found on any portion of the body, and a case is being reported to further support this statement.

The standard textbooks on syphilis, as well as the available literature, have been carefully searched, and no mention is made of a primary chancre of the ear. In a survey of 68 cases of extragenital chancres over a twenty-five year period at the University of Michigan by Wile and Holman,<sup>1</sup> extragenital chancre of the ear is not mentioned.

The case herein presented illustrates the important reality that any unusual lesion can be due to syphilis. This is often overlooked and is probably one of the reasons for the many unexplained positive Wassermann reactions found in routine examinations. With the advent of penicillin it is certainly more important now than it was before to diagnose and treat these lesions as quickly as possible. Every day lost results in a wider dissemination of the spirochete and less chance of an early and permanent cure.

### REPORT OF A CASE

A 25 year old private was admitted to the Army Service Force Regional Station Hospital on June 11, 1945, complaining of a painless lesion in the right ear of two weeks' duration. The lesion started as a small blister, which broke down to form an ulcer. This ulcer first appeared on the right external canal on the concha, but it gradually became larger and spread inward, involving the entire canal. The patient was given local treatment as an outpatient by the eye, ear, nose and throat service for ten days, with no improvement.

From June 11 to 29, the patient was treated in the hospital with local application of several medicaments (20 per cent silver nitrate, sulfathiazole ointment, 2 per cent gentian violet medicinal and boric acid powder). Despite all this treatment, the lesion did not improve. A biopsy was performed on June 27. On June 29 the patient was examined by the dermatologic and venereal disease sections, at which time examination revealed a large, secondarily infected ulcer in the

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From the Medical Service, Army Service Force Regional Station Hospital, Fort Ord, Calif.

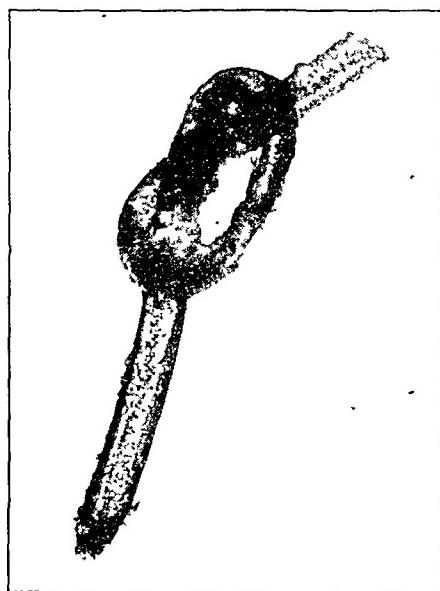
1. Wile, U. J., and Holman, H. H.: A Survey of Sixty-Eight Cases of extragenital Chancres, Am. J. Syph., Gonor. & Ven. Dis. **25**: 58-66 (Jan.) 1941.

Herxheimer reaction during the first day of treatment. The focal reaction consisted of an aggravation of the primary lesion. The ulcer and entire ear became swollen and painful. Further enlargement of the local lymph nodes was noted. The secondary macular rash became brighter in color. The systemic reaction was characterized by chills and fever, the temperature reaching a peak of 103.4 F. The fever subsided in twenty-four hours, and then the temperature remained normal. The ulcer became free of exudate on the third day of treatment, and the cervical lymph nodes became normal on the fourth day of treatment. The entire lesion cleared up completely two days after completion of penicillin therapy (figure, B).

On close examination it was observed that the ends of most of the hairs were broken, showing trichorrhesis and trichoptilosis. One hair appeared to have a small node near the free end. This hair when viewed microscopically was seen to contain the knot shown in the illustration.

The patient was partially deaf and had a cleft palate. No other abnormalities were revealed in physical examination. There was no loss of hair or other abnormality except as described on the scalp. The blood count was normal and the Wassermann reaction was negative.

From November 1945 to the time of writing the patient has used a tonic lotion on the scalp and has had supportive treatment with vitamins. The most recent examination (January 1947) showed a scalp free from scale, considerable regrowth of hair, no trichorrhesis and only a few hairs with longitudinal splitting. Repeated search has failed to show any more knotted hairs.



Trichonodosis of hair.

#### SUMMARY

A case of solitary type of trichonodosis associated with trichorrhesis, trichoptilosis and partial alopecia is reported.

516 Cooper Street.

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#### CUTANEOUS PUNCH

HERMAN GOODMAN, M.D., NEW YORK

Reexamining the files of the *Journal of Cutaneous and Genito-Urinary Diseases* disclosed the following correspondence between Dr. B. A. Watson and Dr. E. L. Keyes in July 1887:

## Editorials

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### PROPOSED DERMATOLOGIC FOUNDATION

The late Bruno Bloch, after a six weeks' trip in the United States in 1928, was asked to write his impressions of American dermatology. He was much interested by what he saw in the various centers visited and commented favorably on the variety and content of the scientific papers that he heard delivered at our national meetings. He pointed out that the educational level and the achievements of the men he met compared favorably with those of his European colleagues, but he deplored the position of dermatology in our medical schools. He emphasized that in this large country with its many excellent medical schools our departments of dermatology did not compare well with the majority in Europe.

If the accomplishments of American dermatology over the past fifty years are critically reviewed, it becomes apparent that they have been attained by the zeal, enthusiasm and hard work of individual dermatologists, while our official status in American medicine has not proportionately advanced.

In every dermatologic center in America, the leaders have been successful practitioners who have devoted a portion of their time to teaching and to purely scientific pursuits. Their private success made it possible for them to visit foreign centers, to attend meetings, to contribute financially to their departments and, at the same time, to advance their personal knowledge. They had the ability to conduct good undergraduate courses. When graduate instruction ceased in Europe because of the wars and young American physicians desiring to specialize in dermatology sought instruction at home, the need for more and better organized departments became apparent. At many schools a valiant effort has been made to furnish adequate instruction, but lack of facilities, such as hospital beds, sufficient numbers of well trained staff men and an adequate budget discouraged and prevented the establishment of departments measuring up to the level that the position of the leaders in the specialty warranted.

American dermatology can no longer rest or be carried along on the laurels and efforts of its leaders alone. The medical schools must realize that what has been accomplished has been by the almost super-human efforts of individuals, and they must be made to realize that dermatology deserves more and better support.

We are not the only specialty that has outgrown its official position. The American Psychiatric Association, at their recent meeting in New

ments of the past century in dermatology were reviewed by Dr. Ormsby, and Dr. O'Leary told the story of syphilis during the past one hundred years. The international outlook in dermatology was pictured in an inspiring address by Dr. R. M. B. MacKenna of Great Britain, a guest of honor of the Section on Dermatology and Syphilology of the American Medical Association.

Dermatology in this country is doing well. It is lusty, it is thriving and it is healthy—and that is particularly gratifying because it has grown from within. No longer is it born of European training. Our own centers are now turning out a constant stream of young men trained both in the basic sciences relating to the specialty and as expert practitioners. As the old practice of apprenticeship training continues to expand, we may confidently foresee the time when the entire country will benefit from the services of well trained, capable dermatologists. The situation will then approach the ideal when more men will devote full time to the study and investigation of the fundamental sciences related to dermatology.

occur in erythema annulare centrifugum, in erythema chronicum migrans, one, and occasionally two, lesions only are found on the lower extremities.

DR. EUGENE F. TRAUB (by invitation): Cases of erythema annulare centrifugum have been thoroughly investigated in the past for any possible cause, and as a rule none is to be found. In other words, foci of infection, allergies and the like, have been suspected, but never proved, to be causes in these cases.

DR. JACK WOLF: Yes, that is true.

#### A Case for Diagnosis (Psoriasis?). Presented by DR. ANTHONY C. CIPOLLARO.

M. L., a salesman aged 41, first consulted the presenter on Jan. 9, 1945. A lesion had developed on the glans penis about three years before. It had healed completely for a time, but about a year ago it recurred and has been present ever since. The patient has been treated with various topical remedies, soothing as well as stimulating, with smallpox vaccine, roentgen rays, grenz rays and ultraviolet radiation. He has been given nicotinic acid by mouth, liver extract by intramuscular injection and calcium by mouth. Friction has been avoided for months at a time. The affected area is constantly covered with a gauze bandage and soothing emollients, lotions, emulsions and the like. The eruption has remained unchanged.

The glans penis shows an exudative, scaly, erythematous and fissured eruption. At times the itching is intolerable. The eruption is now more extensive and exudative than it was originally. The only topical remedy which seems to reduce the exudation and relieve the burning and itching is "noxzema" (a proprietary preparation containing camphor, menthol, phenol, lime water, oil of cloves and oil of eucalyptus in a greaseless base).

#### DISCUSSION

DR. ISADORE ROSEN: I have had occasion to see this patient several times before, when the features of the eruption were much severer. The diagnostic possibilities are chronic exudative dermatitis (contact), psoriasis and so-called erythroplasia. I do not think it is the disease last named, as its clinical features do not coincide with the course of the disease in this case.

DR. FRED WISE: I am not able to offer a clinical diagnosis and believe that a biopsy is indicated, to exclude or confirm the diagnosis of balanitis, psoriasis or erythroplasia of Queyrat.

DR. SAMUEL M. PECK: I have had poor results in treating such patients. I have turned some of them over to Dr. Sachs, because he has developed an apparently successful therapy. I do not believe that the eruption in this case is either psoriasis or erythroplasia; in my opinion, it is a type of chronic balanitis, but I know of no therapy which has been successful.

DR. WILBERT SACHS: It is of little value to discuss therapy until a diagnosis is established. I would suggest the diagnosis of erythroplasia. A biopsy would corroborate this or would exclude other dermatoses, such as psoriasis.

DR. DAVID BLOOM: Although the lesion does not present the typical features of erythroplasia, a biopsy is necessary to exclude this possibility. Like Dr. Scheer, I have seen eczematoid lesions on the penis which proved to be erythroplasia.

DR. HERMAN SHARLIT: Some day, after he has done all he can, some dermatologist will have the courage to place one of these patients in the hands of a clever psychiatrist.

DR. E. W. ABRAMOWITZ: I do not think this eruption is due to a drug. The patient says he is taking nothing but aluminum hydroxide gel. The only drug I know of which could cause this localized dermatitis of the glans penis would be methenamine. The eruption looks like psoriasis. I should like to ask whether any one has seen a case in which erythroplasia turned into cancer.

DR. GEORGE C. ANDREWS: Has the urine been examined?

DR. ANTHONY C. CIPOLLARO: It has repeatedly been found to be normal.

**Scleroderma.** Presented by DR. FRED WISE.

I. G., a man aged 42, was previously presented at the New York Dermatological Society on Oct. 23, 1945. Beginning on November 1, he was given tablets of calcium penicillin, containing 20,000 units each, at three hour intervals, one-half hour before meals, for six days.

**DISCUSSION**

DR. GEORGE C. ANDREWS: I gave penicillin to 2 patients who had a severe and extensive, progressive type of scleroderma. One was a nurse who had previously been thoroughly studied at Mount Sinai Hospital, where she had been in bed for some time. Before I began penicillin therapy, her fingers were almost rigid, and she was not able to use them except as claws. I gave her two courses of penicillin, each one totaling 3,000,000 to 4,000,000 units, in daily doses of 300,000 to 400,000 units for ten days, intramuscularly. Before she left the hospital she was able to do some knitting. She is now actively working as a public health nurse. The other patient, also at Presbyterian Hospital, had a course of 3,000,000 or 4,000,000 units, with great improvement. Later, this patient had another course of penicillin under another physician. I have now lost track of her.

DR. E. W. ABRAMOWITZ: I have recently seen more cases of scleroderma than in former years. The condition of some of the patients is so pitiable that if any money is available for research this disease should receive preference. Physicians interested in peripheral vascular disease see more cases than do we dermatologists, and they are discouraged with present methods of treatment, particularly of patients with systemic involvement. My last patient had stricture of the esophagus and died of cardiac failure. A patient on Dr. Rosen's service who was thought to have scleredema is getting physostigmine bromide, 15 mg. tablets, with apparent improvement. Another patient on Dr. Rosen's service had morphea-like lesions on her left leg. The lesions softened after treatment with physostigmine for one year. Dr. Cipollaro tells me he has had encouraging results with sodium nitrite. Men who have had wide experience with peripheral vascular diseases think none of the vasodilator drugs has any value in treatment of scleroderma.

DR. FRED WISE: Of course the prognosis in the present case is extremely poor, no matter what treatment is administered.

**Squamous Cell Epithelioma of the Lower Lip with Possible Regional Metastasis.** Presented by DR. FRED WISE.

N. S., a man aged 53, registered at the Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital on Oct. 27, 1945, complaining of lesions of two and a half months' duration. He stated that three months ago a pair of pliers fell on his mouth, cutting his lip.

The patient has an extensive induration on the left side of the lower lip about 3 cm. in diameter. On the external surface of the lip there is a lesion 2 cm. in diameter with a central conical depression. On the inside of the lip the mucous surface is irregularly ulcerated, the greatest diameter of the area being 3 cm. There are a palpable submental lymph node 1 cm. in diameter and a questionably enlarged submaxillary node on the left side.

Routine laboratory tests gave normal results. The discharge from the lesion expressed on a slide and stained with the Ziehl-Neelsen method was negative for *Mycobacterium tuberculosis*.

A histologic section, examined by Dr. Charles F. Sims, was diagnosed as "prickle cell epithelioma."

The lesion was excised at the tumor clinic of the Skin and Cancer Unit. The specimen, a V-shaped excision of part of the lower lip, was examined by Dr. A. E. Margulis and interpreted as "squamous cell carcinoma of the skin and mucous membrane, grade I." The section showed a malignant squamous cell neoplasm arising from both the skin and the mucous membrane, at the mucocutaneous junction, and infiltrating the tunica propria and the muscle of the lip deeply, passing

DR. FRED WISE: Confining my comments to the case under discussion, I believe the evidence is much in favor of the cancer following trauma. The man gives a clear history of trauma, followed two and one-half months later by the appearance of a growth and perforation of the lip. An important point is the differentiation of trauma of recent occurrence and trauma of previous long standing. In this case the trauma was of recent occurrence, and for that reason the patient is presented for consideration as to diagnosis and treatment.

**A Case for Diagnosis (Congenital Hypotrichosis and Keratosis Pilaris?).**  
Presented by DR. DAVID BLOOM.

M. F., a man aged 27, is presented from the Skin and Cancer Unit of the New York Post-Graduate Medical School and Hospital complaining of an eruption on the face of a few years' duration, and of alopecia of the scalp and an eruption on the body which have been present since early childhood.

On the upper lip and the chin the patient presents an erythematopustular eruption. The bearded region shows sparse hair and numerous keratotic follicular papules. Similar lesions are also seen on the thighs, abdomen, chest and arms. There is complete alopecia of the scalp in the middle zone, extending from the forehead to the occipital region. The hair on the sides of the scalp is sparse, and there are scaling and folliculitis in these areas. The hair in the axillae and the pubis is sparse.

The patient states that the alopecia and the keratosis pilaris on the body have been present as long as he can remember. The family and past personal histories were essentially unremarkable, except for frequent eruptions in the summer.

Microscopic examination of the hair of the scalp revealed no abnormality.

**DISCUSSION**

DR. HERMAN SHARLIT: I saw this man at the clinic and asked him whether he had ever had roentgen irradiation of his scalp; he said he had, twenty years ago. This factor in the history should be taken into account.

DR. JACK WOLF: If this man received an overdose of roentgen radiation to the scalp, the clinical picture in that location could be explained on that basis. The rest of the clinical picture is only an exaggerated form of keratosis pilaris with involvement of the cheeks, chest and scalp. On the cheeks the process has gone on to the end stage, with loss of the hyperkeratotic follicular plugs and resulting atrophy of the follicles. In the end stage the cheeks remain red. The syndrome of keratosis pilaris with such involvement of the cheeks is referred to by the French as "keratosis pilaris rubra atrophicans facies." I believe the involvement of the upper and lower lips is a complicating folliculitis or an early sycosis.

DR. SAMUEL M. PECK: I agree with Dr. Wolf that the clinical picture is that described by the French school as a keratosis followed by atrophy, but the patient shows two features which I often see after keratosis follicularis. There is a peculiar involvement of the lip, which does not resemble sycosis but is more like seborrhea; this may also be seen on the eyelids. This develops during hot, humid weather; and exposure to sunlight is also a precipitating factor. The lesion does not respond to administration of vitamin A. We now have under observation at Mount Sinai Hospital a mother and daughter with keratosis follicularis. Mere exposure of the daughter's back to large doses of ultraviolet radiation produces a weeping eczematoid eruption which, if it were on the face, one would think was seborrheic dermatitis. I think the case presented tonight would be interesting to study from the viewpoint of vitamin A deficiency. It may well fit into the group of vitamin A dysvitaminoses.

DR. ISADORE ROSEN: When I first saw this man at the clinic, my impression was that he might have a mild form of monilethrix, but this diagnosis was ruled out by the absence of beaded hairs on microscopic examination. The feature which suggested monilethrix was an associated keratosis pilaris over the neck, scalp and face. I believe the condition belongs to the group of congenital ectodermal defects.

DR. E. W. ABRAMOWITZ: To me the disease in this case looks like ulerythema sycosiforme. The patient had some form of treatment to the scalp when a child, possibly roentgen therapy. The bearded region of the face shows an erythematous and pustular folliculitis, which may be an extension of the old cutaneous involvement of the scalp.

DR. JACK WOLF: I think that the disease is nevoid. If it appears chiefly in females, and is sharply limited to the cheeks, is it likely to have anything to do with malformation of the hair?

DR. WILBERT SACHS: The process is generalized. It may be a congenital malformation of the hair follicles and the hair. The sebaceous glands would thus be involved, and that would account for the sebaceous element that is present.

DR. DAVID BLOOM: The patient presents complete alopecia in the central portion of the scalp and sparse growth of hair on the lateral aspects of the scalp. On the body he shows generalized keratosis pilaris, and many of these papules are pierced by a hair. This congenital hypotrichosis belongs to the minor ectodermal defects which are inherited in a dominant mode. No similar abnormality could be found in any other member of the family. The patient also presents sycosis vulgaris of the bearded region, which was benefited considerably by the application of a penicillin ointment.

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CLEVELAND DERMATOLOGICAL SOCIETY

M. T. Ebner, M.D., Vice President

George W. Binkley, M.D., Secretary and Reporter

Nov. 29, 1945

Tuberculosis Verrucosa Cutis of the Neck. Presented by DR. W. W. MURPHY and DR. B. HELD.

Diffuse Idiopathic Atrophy of the Skin Associated with Advanced Pulmonary Tuberculosis. Presented by DR. W. W. MURPHY and DR. B. HELD.

V. S., a white man aged 28, whose paternal grandparents had had asthma, noticed an erythematous lesion on the left shin in 1935. Over a period of several months this lesion thickened, became scaly and finally resolved, leaving an area of atrophic skin. New lesions gradually appeared, enlarged and then coalesced to involve large areas of both lower extremities. In 1942 the forearms and arms became involved in a similar process, while the skin of the lower extremities became more atrophic. Recently the skin of the upper part of the trunk has become involved. For several years the patient has noticed dryness and scaling of the skin of the scalp, face, trunk and soles. The body and pubic hair has fallen; cutis anserina does not occur, and perspiration appears only on the face, palms and soles.

The skin shows a generalized symmetric eruption, most evident on the extensor surfaces of the extremities. The principal lesion is now seen around the shoulder girdle and on the neck and chest and consists of multiple plaques, varying from 1 to 5 cm. in greatest diameter. On the extensor surfaces of the upper extremities are reddish brown areas, varying in size from 2 cm. to large patches on the arms and characterized by atrophy with prominence of the underlying vessels. In some areas the borders can be seen as moderately infiltrated, erythematous bands, about 1 cm. wide, separating the atrophic areas from the adjacent skin. On both lower extremities, from the dorsa of the feet to above the knees, are diffuse areas of brown, atrophic skin, which is thin, without adnexa, loose and covered with thin, dark brown scales, 1 cm. in thickness. Around the knees the skin is thrown into many fine, soft, inelastic folds. The skin of the trunk, face, scalp, palms and soles is dry and shows fine scaling. The body and pubic hair is absent. There is

generalized lymphadenopathy, characterized by flat, firm, nontender, somewhat adherent nodes.

The Kline reaction of the serum was negative. The hemogram and the results of urinalysis were normal.

#### DISCUSSION

DR. E. W. NETHERTON: This case seemed to me to be one of exfoliative dermatitis. Even though atrophy is extensive, there is much exfoliation. The patient has active tuberculosis; one wonders whether the tuberculosis is not a factor in the exfoliative process, even though the cutaneous lesions preceded the manifest pulmonary tuberculosis.

DR. R. E. BARNEY: In addition to the more or less generalized eruption, there were an infiltrated plaque over the right clavicle and some infiltrated nodules on the neck. I believe that tuberculosis plays an important part in the generalized scaly, atrophic dermatitis. I think one may regard this process as a type of pityriasis rubra (von Hebra) occurring on the basis of tuberculosis, keeping in mind that it may have a leukemic basis. It would be helpful to obtain a biopsy of the two types of cutaneous lesions.

DR. W. W. MURPHY: The patient refuses to permit a biopsy of the skin.

DR. H. N. COLE: Several years ago Dr. Driver and I admitted a patient with exfoliative dermatitis to the University Hospitals. Biopsy of specimens of skin revealed the picture of tuberculosis. Large numbers of tubercle bacilli were found in the skin. I think a similar picture may be present in this case, particularly over the clavicles. The atrophic areas could represent an idiopathic type. One sees such atrophy with several other systemic diseases, and I do not see why tuberculosis could not produce it.

DR. J. R. DRIVER: About six months later the patient to whom Dr. Cole refers died of fulminating miliary tuberculosis. I think an attempt should be made to determine the type of tuberculosis which this man has—whether human, avian or bovine. I am of the opinion that it is not human tuberculosis, but avian or bovine.

DR. G. A. DE OREO: Another possible etiologic factor is the lymphadenopathy. The posterior cervical chain of superficial lymph nodes on the left side was most easily demonstrable. He may have tuberculous foci of other parts of the reticuloendothelial system, perhaps of the spleen.

**A Case for Diagnosis (Mycosis Fungoides?).** Presented by DR. W. W. MURPHY and DR. B. HELD.

**Mycosis Fungoides.** Presented by DR. W. W. MURPHY and DR. B. HELD.

**Rhinoscleroma.** Presented by DR. W. W. MURPHY and DR. B. HELD.

M. S., a white woman aged 53, born in Poland, was brought to Cleveland City Hospital in January 1943, for involutional psychosis of paranoid type. At this time there was a small, crusted lesion on the right side of the cartilaginous septum of the nose. This lesion has slowly enlarged.

Examination reveals a sharply defined, firm, pink, crusted tumor extending 5 mm. below, into and occluding the right nostril. It appears to originate from the septum. There is a slight mucopurulent exudate.

The urine was normal. The Wassermann and Kline reactions of the serum were negative. The hemogram was normal. Culture of material from the right nostril yielded gram-positive bacilli and *Staphylococcus aureus*. Histologic examination revealed elongated, anastomosing stratified epithelial cells, forming a framework. Within the interstices was infiltration with lymphocytes, Mikulicz cells, neutrophils and plasma cells. There were also numerous acidophytic, hyaline degenerated cells of Pallizari.

Roentgen therapy is being given. Sodium penicillin, 15,000 units every three hours for two weeks, has been administered. No change has been noted.

## Book Reviews

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**The X-Ray Treatment of Accessible Cancer.** By D. Waldron Smithers, M.D. Price, \$8.50. Pp. 147, with 101 illustrations, including colored plates, diagrams, charts, 21 tables and 12 graphs. Baltimore: Williams & Wilkins Company, 1946.

This volume is a compilation of the author's personal experiences with the roentgen ray treatment of malignant diseases of the skin and adjacent mucous membranes. Like other workers in this field, the author believes that with a combination of surgical treatment and radiotherapy it should be possible to cure all cases of accessible cancer. He discusses the merits of both surgical and radiation therapy but concludes that for several reasons roentgen radiation properly applied is superior to surgical treatment in most instances.

Two procedures described in detail are noteworthy. The first of these is the utilization of tumor cell counts to follow the progress of the response of the neoplasm to radiotherapy. Serial biopsies are performed before radiation and at intervals during radiation, daily at first and at longer intervals as the tumor recedes. The numbers of the differentiating, resting, degenerating and mitotic cells are plotted on graph paper, and curves are drawn. Mitotic cells disappear within a few days after radiation is begun. As a result of the radiation the degenerating cells gradually increase in number, the resting cells decrease, and, during the period of recovery from the effects of radiation, the differentiating cells gradually increase. These changes are well illustrated with colored photographs and charts.

The other notable procedure is the logical utilization of radiations of different wavelengths to distribute the maximum effect of the radiations as evenly as possible throughout the tumor mass. Most dermatologists and radiologists employ approximately the same quality of radiation throughout the treatment of a particular neoplasm. Smithers usually begins by using 200 kilovolt apparatus and then changes to 100, 60 or 45 kilovolt apparatus. In many instances 6,000 to 8,000 r are administered in about eighteen days.

The classification of accessible cancer is the usual one, but the division of the extent of the disease into stages is another new idea. Staging helps physicians to select the proper therapy and to foretell changes in the tumor and in the condition of the patient.

Concise and well illustrated, the book includes eleven chapters, an appendix containing definitive terms and useful isodose curves, a bibliography and author and subject indexes. The paper, printing and illustrations are of fine quality.

This work should be in the library of all who are interested in the problem of cancer and should be particularly valuable to any one using roentgen rays for the treatment of malignant diseases of the accessible parts of the body.

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## News and Comment

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### GENERAL NEWS

**Application for Space in Scientific Exhibit.**—Fellows of the American Academy of Dermatology and Syphilology who wish to apply for space in the Scientific Exhibit at the Chicago meeting of the academy in December 1947 are requested to write for an application blank to Dr. Marcus R. Caro, 25 East Washington Street, Chicago 2, Illinois.

our community that we inform one another of errors made and of further developments in our transferred private patients just as we do in the clinic. In thanking my colleagues for such help given me I believe that I am speaking for you all, for in this sphere of mutual education we are all dependent on one another.

In the course of my work in our specialty I have become aware of many thoughts stimulated by my experience with patients and with other dermatologists. These random thoughts have accumulated over the years and have gradually arranged themselves into a definite pattern. Undoubtedly this pattern, or philosophy, that each of us develops on the basis of his own experience becomes the determining influence in his approach to the medical problems that confront him. I am certain that the thoughts which I have accumulated I own in common with most dermatologists. In giving them voice, therefore, I feel that I am speaking for many of you, especially when I discuss the role of the clinician in modern dermatology.

In these days of great scientific advances in medicine, the term clinician has come to carry with it the stigma of negativity. When a physician's obituary notice is being written and there are no scientific accomplishments that can be credited to his life, when he has written nothing of importance and has taught no one, there is always the modest statement that he was a good clinician. The term seems to carry with it the somewhat contemptuous connotation that, in the absence of other medical virtues, the physician had patients and they somehow got along well. Actually, in correct usage, the term clinician is one deserving of honor. It denotes a physician who studies diseases at the bedside or in actual contact with the patient. The great clinicians are those whose studies of disease are directed into channels of constructive investigation by the stern discipline of having as their taskmaster a person who is sick. A clinician does not merely practice the art of amelioration of symptoms. He is a painstaking searcher for all the physical signs and symptoms that may point to an eventual diagnosis. He must be familiar with all forms of laboratory investigation that may add significant clues. Above all he is a physician treating a patient, and he must evaluate wisely the entire case before him.

Most of the dermatologists of previous generations received their primary training in our specialty by acting as assistants to older dermatologists. During such apprenticeship, which in many cases was extended into permanent association, the students were able to observe at close range the methods of study and work that their preceptors had developed through years of experience. Often the philosophies and methods of practice had been handed down through several generations of dermatologists with extensive development by each, and the apprentices were benefiting by close contact with a great heritage. If the preceptors were themselves well versed in pathology, mycology, bac-

how much this great clinician was able to recognize and describe by the mere use of his powers of observation. More amazing is the tremendous amount of his teaching that is still valid in spite of the continuous attacks of time and progress against its stability. Hebra's description of psoriasis leaves little to be added even today. In discussing the treatment of psoriasis he included most of the internal and local medications that we still find useful, and he appraised them with a wisdom that would be enviable even in our advanced time. In introducing the section on the treatment of psoriasis, for example, he stated<sup>1</sup>:

For the cure of psoriasis, and indeed of chronic diseases of the skin generally, two methods have from early times been proposed. The first of these started from the supposition that all the chronic dermatoses are children of one parent, the products of one and the same dyscrasia or morbid change in the blood; and, therefore, that these diseases are to be cured by purifying and correcting the state of the circulating fluid, or by expelling acrid matters. For the practice of this mode of treatment, no accurate diagnosis was required. . . . The unsatisfactory results yielded by this plan led physicians to enter upon an entirely different path, that of experiment and observation. Now this path is, I must confess, the one which I myself follow exclusively in the treatment of cutaneous affections and indeed of disease in general. I set not the slightest value on any remedies except those which (after repeated trials and when I am accurately acquainted with the complaint) I find to produce a favorable change in its course or, in other words, to cure the patient. I never attribute therapeutic powers to a medicine unless I observe its employment to be invariably and constantly followed by some change in the morbid products and by the termination of the disease in a shorter time than when it is allowed to undergo spontaneous involution.

In these days of blanket diagnosis and routine systems of treatment when the proponents of the all-embracing concepts of neurodermatitis and psychosomatic disease are attempting to break down distinctions between diseases and to sweep them all into amorphous modern versions of the ancient humors and dyscrasias, Hebra's voice is sadly needed.

On the subject of scabies Hebra the clinician wrote a chapter to which nothing need be added (with the exception of benzyl benzoate) to bring it up to date in 1947. At a time when scabies had been universally treated as a systemic disease, with sufficient lack of success to make it the most common of all diseases of the skin, he determined by extensive experiments that scabies was caused by the local action of the itch mite, confirming the forgotten discovery of Bonomo in 1687. His description of the various clinical features of scabies, the life cycle of the itch mite and the various methods of treating the disease produced one of the classics of medical literature.

To the complex study of eczema Hebra brought the revolutionary knowledge, evolved from experimentation with external irritants, that

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1. Hebra, F.: On Diseases of the Skin, London, The New Sydenham Society, 1868, vol. 2 p. 19.

final stage of his training there is no better finishing school than the association with a qualified preceptor. It is to be hoped that additional preceptorships will be established, so that in time every student will have the benefit of this type of guidance.

Since our aim in training dermatologists is primarily to develop good clinicians, it necessarily follows that our teachers must be good clinicians. To help students to develop those powers of observation and reasoning that are necessary for good clinical judgment, a teacher must himself be the master of those virtues. He must be able to point out all features of a disease and to appraise them objectively if he is to train good clinicians. He must also practice what he teaches. If his interpretation of clinical findings is based on unfounded theories or is influenced by his own emotional difficulties, or if his practice is tinged with fads, his students will either follow him blindly into uncharted seas or they will disbelieve all he teaches. It is a heavy burden to have the responsibility of helping to mold an inexperienced mind. It is a responsibility not to be assumed lightly or capriciously. The preceptors of old chose their apprentices with care, so that the few opportunities available were given to men who were thought capable of using them well. For the sake of the students of today the same care should be exercised everywhere in selecting the few who are to teach them. By the proficiency of the teachers and preceptors who are chosen and by the quality of instruction which is given we are fixing the level of the dermatologists who will follow us.

Finally, what is the role of the clinician in the investigative field? It is true that most epoch-making advances in science have been made in the field of pure research, that is, research not directly applied to some practical end. But even pure research, as exemplified by the problem of nuclear fission, was spurred to successful completion years ahead of its time by the practical necessity of producing an atomic bomb in a competitive race for time. So in the field of dermatology many important contributions were made with the direct aim of clinical application. To mention but one, Ehrlich performed his ingenious experiments with organic arsenicals in a deliberate search for a drug to destroy *Treponema pallidum*.

Often great discoveries have had their origin in accidental observations. Fleming's chance discovery of the antibiotic action of the mold *Penicillium* would have been just another interesting observation were it not for the utilization of this phenomenon in clinical medicine. By its extensive exploitation in all fields of medicine this discovery ushered in a completely new era of antibiotic therapy that still has many developments to unfold.

In 1895 Roentgen noticed that radiations from a Crookes tube produced fluorescence in a piece of paper coated with barium platin-

and that placing a patient with heart failure on his back merely moved the fluid from the lower to the upper part of the body. It is only in the last few years, however, that these obvious truths have been recognized, and such patients are now being treated more successfully by being kept in a chair during the day and propped up in a tilted bed at night. This clinical reorientation was the contribution of Samuel A. Levine, whose recent paper, "The Treatment of Congestive Heart Failure,"<sup>3</sup> I can recommend as stimulating reading even for dermatologists, for it is a masterly exposition of the importance of clinical observations in differential diagnosis that could well be transposed into our own work.

In all research having as its aim the solution of clinical problems, good clinical judgment must be relied on to guide the work. How can one evaluate the effect of various treatments on, let us say, cases of neurodermatitis if eventually there is some question about the actual diagnosis in the cases under scrutiny? Investigations into causative factors in cases of supposed cutaneous allergy, for another example, can have but little value if the patients are discovered later to have been suffering from scabies, pityriasis rubra pilaris or some other nonallergic disease. Finally, a clinician must be "accurately acquainted with the complaint" in all its many clinical variations before he may correctly evaluate the effect of the experimental factors that he has introduced.

In dermatology, as in all fields of medicine, it is the privilege of the few to make discoveries that will bring benefits to unknown multitudes. It is, however, the opportunity of every dermatologist to bring comfort and relief from suffering to each of the individual patients with whom he has personal contact. This opportunity carries with it the responsibility to make himself skilled in all methods of diagnosis and treatment that may qualify him for this task, the duty to make of himself a good clinician.

1905 Field Annex Building.

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3. Levine, S. A.: The Treatment of Congestive Heart Failure, Proc. Inst. Med. Chicago **16**:214, 1946.

In 1924 Bordier<sup>7</sup> recommended diathermy for the removal of superfluous hair. Kovacs<sup>2</sup> stated that the principle of the action in all high frequency electrosurgical methods is an intense concentration of current under a small active electrode. This results in a destructive thermal effect around the needle, which leads to instantaneous coagulation of the albumin of the tissues.

According to some investigators, diathermy allows the operator to remove the hairs more rapidly, with less pain and with good cosmetic results. Rosenberg and Smith<sup>8</sup> were of the opinion that the cutting current resulted in less scarring than that produced by electrolysis, and they considered that there was little chance of recurrence as the greatest amount of heat was concentrated at the point of the needle, which should be inserted into the hair papilla. Karp,<sup>9</sup> Goodman<sup>10</sup> and Derow<sup>11</sup> stated that surgical diathermy had a "cone effect"; i. e., the burned area was in the shape of a cone radiating from the point of the needle, and thus the papilla could be destroyed without scarring even if the point of the needle was only near the base of the hair follicle. Gross<sup>12</sup> doubted that the "cone effect" occurred but stated that diathermy was relaxing to the operator and gave good cosmetic results. Gara<sup>13</sup> preferred coagulation by long wave diathermy. He used a bipolar current at 10 to 60 milliamperes for one to two seconds. He noted that recurrence varied from 20 to 40 per cent and at times to 60 per cent, with an average of 30 per cent. Karp,<sup>9</sup> Derow<sup>11</sup> and Lerner<sup>14</sup> stressed the fact that there was little or no recurrence in their patients. All the advocates of the diathermy method claimed that there was practically no scarring when operators used the proper machine and technic. Savill,<sup>15</sup> on the other hand, favored electrolysis over diathermy for the removal of hair. She acknowledged that recurrence may be as frequent with electrolysis but stated the belief that scarring is more likely to ensue after diathermy.

7. Bordier, H.: Technique de l'épilation diathermique, *Monde méd.*, Paris **42**:78-81 (Feb. 1) 1932.

8. Rosenberg, W. A., and Smith, E. M., Jr.: Removal of Superfluous Hair with the Cutting Current, *Arch. Phys. Therapy* **24**:277-279 (May) 1943.

9. Karp, F. L.: High Frequency Current in the Treatment of Hypertrichosis, *Arch. Dermat. & Syph.* **43**:85-91 (Jan.) 1941.

10. Goodman, H.: Non-Surgical Reparative Dermatology or Electro-Medical Cosmetology, *Urol. & Cutan. Rev.* **46**:726-727 (Nov.) 1942.

11. Derow, D.: Short Wave Epilation, *Arch. Phys. Therapy* **20**:101-102 (Feb.) 1939.

12. Gross, P., in discussion on Lerner.

13. Gara, G.: Hypertrichosis: The Problem and How to Handle It as It Appears in the Every-Day Practice, *Urol. & Cutan. Rev.* **45**:771-774 (Dec.) 1941.

14. Lerner, C.: Essentials in the Art of Epilation for Hypertrichosis, *M. Rec.* **151**:193-194 (March 20) 1940; The Treatment of Hypertrichosis by Electro-coagulation, *New York State J. Med.* **42**:879-882 (May 1) 1942.

15. Savill, A. F.: *The Hair and Scalp: A Clinical Study, with a Chapter on Hirsuties*, London, Edward Arnold & Co., 1935, p. 274.

on intermediate hair, but with weaker currents and terminal hairs the time might have to be increased to sixty seconds. The average interval required to pull the hair out and reinsert the needle was approximately five seconds. In one-half hour about forty hairs could be removed.

#### EXPERIMENTS WITH AN ANIMAL

**EXPERIMENT 1** (electrolysis).—The hair of a full-grown rat was shaved with an electric razor. The rat was anesthetized with veterinary pentobarbital sodium and was placed on the moistened positive electrode. The needle was inserted 2 or 3 mm. at a right angle to the surface into the skin in the shaved area. One milliampere of current was applied for thirty to sixty seconds. A biopsy was made immediately and the sections stained with hematoxylin and eosin.<sup>17</sup> Although the specimen was cut serially it was difficult to find the track of the needle, because the changes produced were not prominent. Only the areas showing the most advanced changes are portrayed in the photograph.<sup>18</sup> The lesion was almost as large as a high power field. The epidermis was attached and the cell borders indistinct. Some pyknotic nuclei were visible. In the center of the altered area the collagen had a blue tinge and contained granular strands and cell debris. Surrounding this area the tissue was more eosinophilic and contained many cells with nuclei which were slightly distorted and more basophilic than the nuclei of the normal cells (fig. 1A).

**EXPERIMENT 2** (intermittent monopolar short wave).—The needle attached to the coagulating pole of the short wave machine was inserted 2 to 3 mm. into another shaved area of the same rat in a manner similar to that in experiment 1. The rheostat was set at "r," and ten to twenty half-second exposures were given. A biopsy was made, and the sections were stained with hematoxylin and eosin (fig. 1B). The affected area was saucer shaped and slightly larger than a high power field. The cells of the epidermis were deep blue, and most of the nuclei could not be delineated. The collagen was of a deep basophilic color in homogeneous broad ribbons or chunks, containing only a few pyknotic nuclei.

**EXPERIMENT 3** (continuous monopolar short wave).—Monopolar continuous one second exposures with the same settings as in experiment 2 resulted in similar lesions with more severe changes. The collagen bundles were confluent and more basophilic than in experiment 2. The shape of the lesions was the same as that of the lesions caused by multiple shorter exposures.

**EXPERIMENT 4** (bipolar short wave).—The same exposures were given as in experiment 2. The same severe alterations in the cutis resulted as those observed in experiment 3, but the changes were over a larger area (three fourths of a low power field).

#### EXPERIMENTS WITH HUMAN SUBJECTS

In the experiments with human subjects, tissue was obtained at autopsy from the pubic area. Two adjacent circles, A and B, were drawn with ink on the skin. The monopolar short wave was applied to hairs for a half-second or less for ten to twenty exposures in circle A, and in circle B hairs were treated with electrolysis with  $\frac{3}{4}$  milliampere for about forty to sixty seconds. Treatment was

17. The serial sections were made in the Department of Dermato-Histopathology of the Johns Hopkins Medical School.

18. All photographs were taken to show the most severe changes caused by the different modes of current.

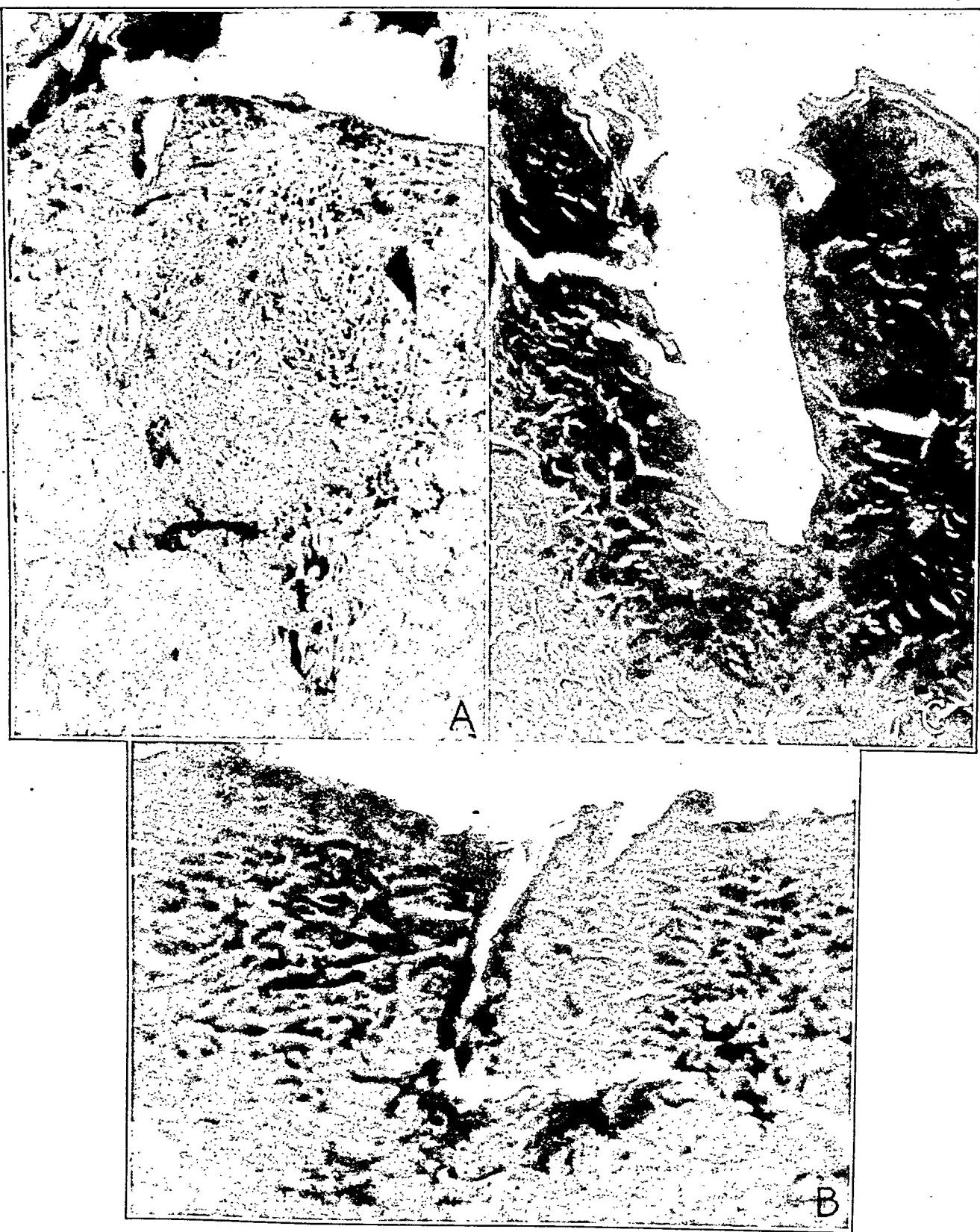


Fig. 1 (rat tissue).—*A*, mild destructive changes from the electrolysis. The true architecture of the skin is readily discernible. *B*, extreme burning of the tissue in the shape of cylinder with the needle as the axis from the vacuum tube type of high frequency current. *C*, destruction of the desiccated tissue by spark gap high frequency current similar to that obtained with the vacuum tube machine.

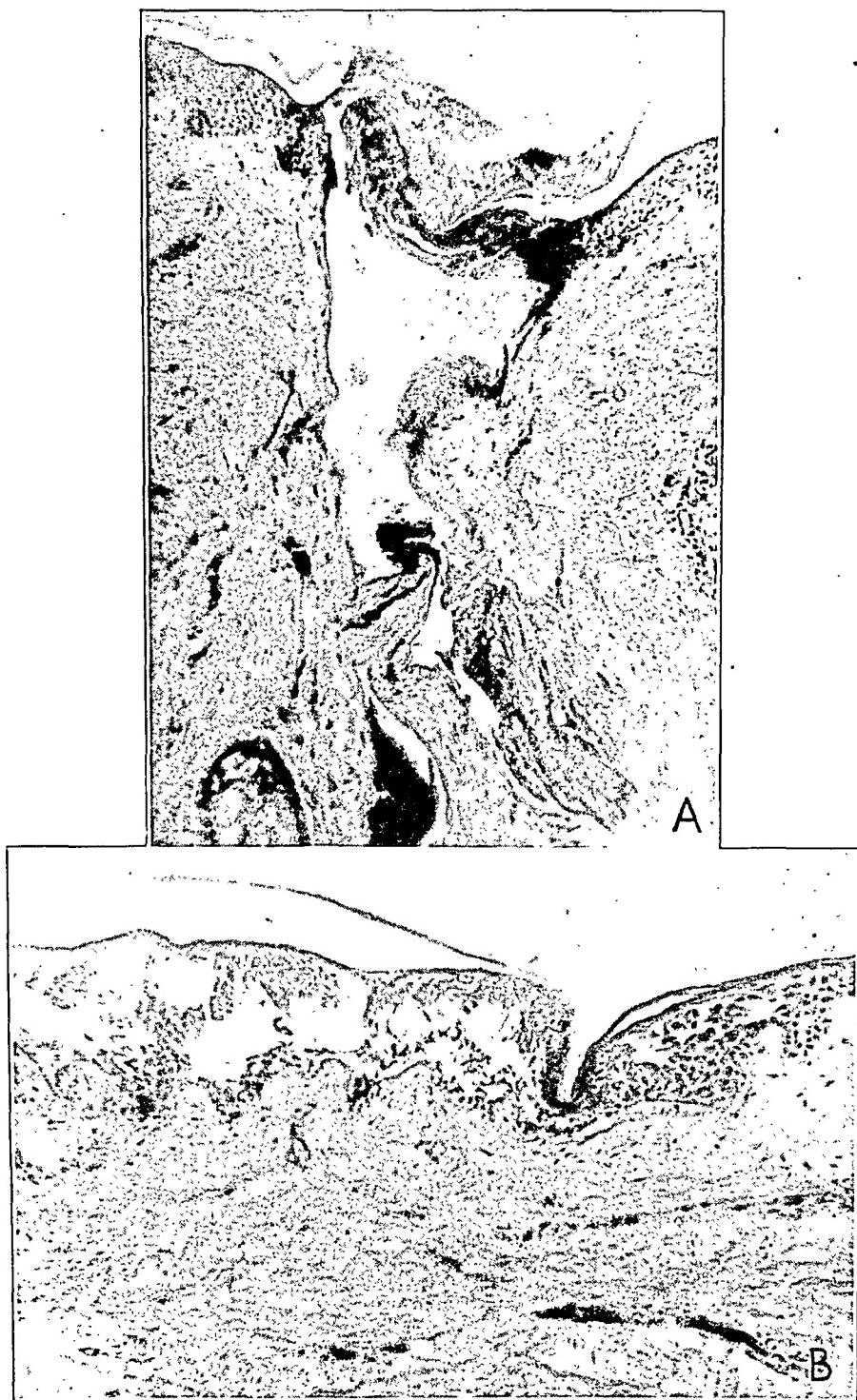


Fig. 2 (human tissue).—*A*, the follicular destruction resulting from the use of electrolysis is confined principally to the follicle and its orifice. The perifollicular alterations are mild. *B*, a nonfollicular lesion resulting from treatment with electrolysis shows a wide zone of edema and a small area of destruction of the epidermis surrounding the puncture from the needle. The alterations in the collagen are mild.

In the area through which the needle passed, i. e., through the follicular canal and out through the base of the follicle, the histologic changes were as follows: The epidermis in the follicular orifice and for a distance of about 460 microns in diameter was depressed and distorted (fig. 2 A). It contained narrow bands of dark blue conglomerate masses of pyknotic nuclei. The follicular wall was replaced by a fine granular, slightly basophilic core of material. These changes extended down through the racemose sebaceous gland under the follicle. In a nonfollicular lesion, surrounding the depression where the needle was introduced, the epidermis for about 1,000 microns was edematous and contained intraepithelial vesicles (fig. 2 B). Below the epidermis the burned core of collagen was approximately the same width at the bottom as at the top, i. e., about 500 microns.

*Short Wave.*—In an adjoining area of skin on the same subject about eight hairs were treated with the vacuum tube machine with a monopolar coagulating current with ten to fifteen approximately half-second exposures and others by continuous two second exposures. The needle was inserted also into several nonfollicular areas, which were given continuous two second exposures at the same setting. A specimen for biopsy was taken from the treated area, was fixed in a solution of formaldehyde, stained with hematoxylin and eosin and cut serially in the same manner as the specimen from the area treated with electrolysis.

A treated hair follicle showed the following changes: The mouth of the follicle was wide, and the rete cells were not altered, but in the canal the lining cells were shrunken and had pyknotic nuclei or were replaced by a vesicle. The follicular wall was incompletely destroyed. The perifollicular tissue was unaltered, but the cells in the center of the underlying sebaceous gland showed signs of lysis, and the collagen below the gland was in basophilic bands (fig. 3 A).

Histologic examination of a nonfollicular lesion caused by high frequency generated by the vacuum tube machine showed the following features: The surface of the epidermis was depressed in the shape of a shallow funnel about 200 microns wide and about 160 microns deep. The rete cells lining this depression were shrunken so that little cytoplasm was seen and the nuclei were pyknotic. In the epidermis, in an area about the depression 830 microns in diameter, there were many small intraepithelial vesicles. Extending down through the dermis to the level of the sweat glands there was a zone of basophilic collagen, which was approximately 500 microns wide throughout its length. The collagen was in basophilic bands or chunks (fig. 3 B).

#### EXPERIMENTS WITH HIGH FREQUENCY CURRENTS GENERATED BY SPARK GAP MACHINES

Experiments with the high frequency current generated by spark gap machines were confined to the rat's skin or to small human tumors before their complete removal and to the skin of a few clinical patients who were treated for the removal of hair. Two different makes of machines were used. The lesions which resulted were of the same general shape, intensity and quality as of those due to short wave. About 10 microns of tissue immediately around the needle had a tendency to stick to the needle and pull away when the electrode was extracted (fig. 1 C):

always possible for even an experienced operator to be certain that the needle is inserted too far or not far enough.

Two types of insulators have been used. One is a sheath over the needle excluding the point, and the other is a coating on the needle leaving the point of the needle exposed. Needles covered by sheaths frequently break at the point where the needle leaves the sheath. A sheath increases the diameter of the needle, and it is difficult to insert it into the follicle. A coating of insulation increases slightly the diameter of the needle, but with use the coating wears off. If the insulating material is colorless, it is difficult to determine how much of the needle is coated or how deeply the needle is inserted. These additional sources of error may increase the number of hairs that recur after treatment.

#### REPORT OF CASES

In an editorial in the *Journal of Clinical Endocrinology*<sup>20</sup> it is contended that: "Electrolysis is an unending business and apt to be scarring if the beard is at all luxuriant." The following 2 cases are reported to illustrate that satisfactory results can be obtained with electrolysis in patients with severe hypertrichosis (terminal type of hair) if the patient perseveres and if the operator is careful.

CASE 1.—A patient with severe hypertrichosis (terminal type of hair) involving the mandibular regions and the front of the neck was treated with electrolysis once a week from June 1938 to December 1940 for a total of seventy hours. From 1940 to 1943 she received seven treatments to destroy the hairs that had recurred. Only slight scarring resulted. She was able to tolerate 1½ milliamperes of current. Before treatment was started, the patient shaved or spent half an hour a day rubbing an emery board over her face to control the growth of hair, but after treatment there was no return of the terminal type of hair.

CASE 2.—A patient was not able to tolerate electrolysis with more than ¾ millampere of current. It was difficult to determine just how much hair of the terminal type was present, because she used depilating wax each week to remove the protruding hairs. She was treated from November 1941 to October 1944 for a total of eighty treatments. In 1945 she returned once a month for the purpose of having an occasional slight regrowth destroyed, whereas previously the hair on the chin and neck was so excessive that it could be treated each week. No visible scars are present. If the patient had been able to tolerate treatments of 1½ milliamperes of current, half the number of sessions would probably have given satisfactory results.

The question of pain is important in the treatment of patients with hypertrichosis. If a patient tolerated electrolysis therapy poorly, she usually complained of much pain or discomfort when treated with the diathermy current. Some patients seemed to have no discomfort. Many of them complained of some pain in the first treatment. The

20. The Endocrine Puzzle of Heterosexual Hypertrichosis (Hirsutism), editorial, J. Clin. Endocrinol. 3:426-427 (July) 1943.

it is suggested that patients return at regular short intervals so that the regenerating follicle can be treated before it attains its full growth.

#### SUMMARY AND CONCLUSION

Comparison of histologic changes caused by treatment with diathermy and electrolysis showed that the alterations in the epidermis were similar in shape but were more intense or severe after treatment with diathermy. The rete cells of the follicle could be destroyed as completely by treatment with high frequency as with electrolysis, but with the former agent the cells were replaced by a denser more basophilic material and the changes seemed to be more destructive and irreversible.

Most of the hairs removed with high frequency currents recurred unless the current was sufficiently intense or was applied long enough to cause visible burns which tended to heal with depressed scars.

The lesions caused with high frequency currents took the shape of a cylinder and not that of a cone.

NOTE.—Dr. Murry M. Robinson (Removal of Superfluous Hair by Monopolar Coagulation, *M. Ann. District of Columbia* no. 11, 15:531 [Nov. 1946]) stated that with the diathermy current he has demonstrated that a cone effect is obtained. "The 'coagulation' forms a cone with the apex at the point of the needle and the base at the surface of the skin, so that with a steadily applied current, destructive action will occur at the surface of the skin and produce visible scarring; whereas with the current applied in short bursts the action takes place only at the papilla and its immediate surroundings, and the surface of the skin is left unaffected." Unfortunately, his photomicrographs do not demonstrate the cone-shaped area of destruction.

8 East Madison Street.

#### ABSTRACT OF DISCUSSION

CAPTAIN ROBERT L. GILMAN, Memphis, Tenn.: I do not believe that Dr. Ellis needs to apologize or be diffident in the opening of his paper because it concerns a process that, no doubt, all of us, without exception, have used. I do not imply that we have been familiar with it, but we have certainly used it with familiarity.

I was struck by Dr. Ellis' conclusions, which I arrived at by a different route, as many of us have. Dr. Ellis seemed to be the first investigator to prove by painstaking work his point that treatment with electrolysis is superior to treatment with diathermy in the permanent removal of hair. That has been my observation.

I note that he had less recurrence and fewer complications with electrolysis. After removing pigmented hairy moles with the short wave machines, satisfactorily and without leaving a disfiguring scar, I have observed that many times a few hairs will remain, regardless of the amount of current used.

at a time, and, second, when more than one needle is used there is an unequal distribution of current among the several needles. If thirty-six needles are used, as recommended by at least one person, the current in one needle may be one hundred times stronger than in an adjacent needle. Therefore, in addition to the technical difficulty of controlling more than one needle at a time there is an objection to the use of multiple needles based on distribution of current.

For routine purposes I advocate the use of high frequency current for the treatment of patients with hypertrichosis. However, the most important thing, to my mind, is to have equipment which is manufactured for this specific purpose. Many dermatologists make the mistake of thinking that any equipment for the use of high frequency current is suitable for treatment of patients with hypertrichosis. It is not, because in some equipment the current cannot be cut down enough to destroy the follicle without also destroying a great deal of surrounding tissue.

Also, a biterminal electrode should be used. The disperser electrode can be held in one hand, since the active electrode is the needle.

Dr. Ellis has mentioned that it took fifteen seconds to destroy some hair follicles with one type of diathermy apparatus which he used. I think that this type of apparatus is entirely unsuitable for such work. It should not take more than one or two seconds to destroy a hair follicle when the proper machine and the proper current are used. I base this statement on results which I have had during the last fifteen years using different types of high frequency currents.

I prefer high frequency current to galvanism for the treatment of patients with hypertrichosis because with high frequency currents more hairs can be removed per unit of time. I have not seen an abscess or a furuncle develop in a patient when the work has been properly done, either by me or by my associates at the New York Skin and Cancer Unit.

Treatment with either galvanism or high frequency currents causes pain. However, with high frequency currents the pain lasts for a second or so, whereas with galvanism the pain is less intense but is prolonged over a period of fifteen to forty-five seconds.

The matter of recurrence is important. So far as I am able to determine, there is no difference between treatment with high frequency current and with galvanism in the amount of hair which recurs. There is no way in which we can accurately determine the amount of hair which grows back. My guess is about 20 per cent after either method of treatment.

I am glad that Dr. Ellis has shown that there is cylindric destruction of tissue about the active electrode. I have already elaborated on that point. Scars can be severe with galvanism as with high frequency currents, but prevention of scars depends on the critical control of currents. Partially insulated or platinum needles offer no practical advantages. Needles made with jeweler's steel, such as are commonly used, have been satisfactory to most operators.

I do not doubt that hair can be successfully removed without causing scars with either the galvanic or the high frequency currents. However, the technic has to be faultless, and, unfortunately, not all dermatologists have taken the trouble to become experts in this phase of physical therapy.

I should like to take the opportunity here of condemning once more the use of roentgen rays, radium and other radioactive agents for the removal of superfluous hair. I want to emphasize it at this time because there are now, in Detroit and Chicago, establishments where superfluous hair is removed with roentgen rays. It seems to me that this is a revival of the old Tricho Institute

## VITAMIN A IN DARIER'S DISEASE

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SINCE the first description by Darier<sup>1</sup> in 1889 more than three hundred and fifty papers have been published dealing with Darier's disease, a relatively rare condition, the cause of which, in spite of numerous investigations, remains undetermined. New knowledge of vitamin deficiency states brought promise of a fresh attack on the problem. Peck, Chargin and Sobotka (1941),<sup>2</sup> having noted the resemblance between the appearance of the skin in naturally occurring vitamin A deficiency and Darier's dyskeratosis, treated a patient with vitamin A and reported improvement. Since then many other patients have been similarly treated, many with benefit. The object of this paper is to describe our studies on the effect of vitamin A in 7 cases of Darier's disease and to compare our results with those of others. Brief notes of our own series of cases are as follows:

### REPORT OF PRESENT SERIES OF CASES

CASE 1.—Mr. S., aged 33, had suffered from trouble with his skin since childhood, but otherwise his health was good. No other member of his family was affected so far as he knew. Examination showed typical Darier's disease, with pigmented, keratotic, partly follicular papules scattered over the body and limbs. They were most numerous on the neck, shoulders and sides of the trunk. Warty lesions were present on the backs of the hands. After three months' treatment with vitamin A many pigmented, keratotic plugs had disappeared, while others were smaller and lighter in color. The wartlike lesions on the backs of the hands remained unaffected, however. This man was then passed into the Navy as perfectly fit.

CASE 2.—Miss S., aged 30, has had trouble with her skin all her life. The appearance was that of severe Darier's dyskeratosis. The skin was dry, and

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From St. John's Hospital for Diseases of the Skin, London, England.

1. Darier, J.: De la psorospermose folliculaire végétante, Ann. de dermat. et syph. **10**:597, 1889.

2. Peck, S. M.; Chargin, L., and Sobotka, H.: Keratosis Follicularis (Darier's Disease): Vitamin A Deficiency Disease, Arch. Dermat. & Syph. **43**:223 (Feb.) 1941.

CASE 6.—Miss P., aged 19, when first seen had the characteristic firm, pinhead-sized to pea-sized, brownish papules on the neck, legs and arms, but none were present on the trunk. There were wartlike lesions on the backs of the hands, and papules were visible on the palate. An eruption of bright red, discrete papules was present on the chest, having appeared there only three weeks previously. Her position in the family is shown in figure 3.

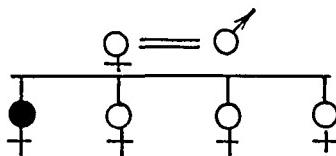


Fig. 3 (case 6).—The familial position of Miss P. is shown by the black disk.

This case is the only one in which improvement has been great, including regression of the warty lesions on the backs of the hands. This patient, it should be noted, is also the only one treated within one year of the development of trouble with the skin. After seven months' treatment only three pigmented papules could be found; these are on the right temple.

CASE 7.—Miss D. was 13 years old. Her family tree is shown in figure 4, no other members of the family being affected. Pigmented papules were numerous

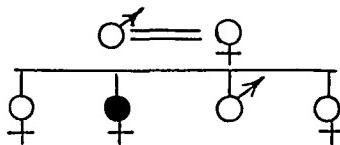


Fig. 4 (case 7).—The familial relationship of Miss D. The patient is indicated by the black disk.

and well marked on the neck, shoulders and limbs, the backs of the hands showing the usual wartlike lesions. Papules were present on both hard and soft palates.

The table shows that of 7 cases, great improvement with vitamin A therapy occurred in 1, much in another, slight in 3 and none at all in 2. Of the 2 patients who did not improve, 1 continued treatment for one month only (case 4), probably too short a time for benefit to appear. The other (case 5) persisted with treatment for three months, when she had taken 9,000,000 international units of vitamin A without result.

It was possible to estimate the vitamin A and carotene levels in the plasma in 4 cases before treatment was begun. The figures were all within normal limits. Dark adaptation tests carried out in 5 cases before any vitamin A was administered all gave curves somewhat outside the normal range.

#### TREATMENT

Big doses of vitamin A, in the neighborhood of 100,000 units daily, seem to produce the best results, and it is suggested that they should be continued until improvement ceases. With such quantities there appears to be no danger of ill effects from overdosage; 1 of our patients (case 3),

a child of 9 years, took 100,000 international units daily for ten months, without any sign of toxic symptoms.

The treatment should be continued for at least two months. This is necessary because some patients respond to vitamin A slowly and their conditions might be considered hopeless if treatment were abandoned too early. Once maximum benefit has been achieved it appears that the dose may be reduced to 30,000 units daily.

Since it had been shown by Mandelbaum and Schlessinger (1942)<sup>3</sup> that vitamin A can be absorbed through unbroken skin, an ointment containing 5,000 international units of vitamin A per gram was rubbed into a badly affected area on the patient in case 4 for one month. It was hoped that the possibility of high concentration of the vitamin A in the skin produced by inunction might have a good result, but this was not found to be so, as no beneficial effect was noted.

#### COMMENT

That vitamin A therapy has beneficial, sometimes even striking, effects in cases of Darier's dyskeratosis can hardly be doubted. The role of vitamin A, however, in Darier's disease is still under discussion. Apart from our own cases, improvement after vitamin A therapy has been recorded by Peck, Chargin and Sobotka (1941)<sup>2</sup> in 4 cases; Barwasser (1941)<sup>4</sup> in 1 case; Cannon (1941)<sup>5</sup> in 1 case; Sweitzer (1942)<sup>6</sup> in 1 case; Michelson (1942)<sup>7</sup> in 1 case; Abramowitz (1942)<sup>8</sup> in 1 case; Peck, Glick, Sobotka and Chargin (1943)<sup>9</sup> in 9 out of 10 cases (4 of which were reported by Peck, Chargin and Sobotka in 1941); Newman (1943)<sup>10</sup> in 1 case; Carleton and Steven (1943)<sup>11</sup> in 2 out of 4 cases,

3. Mandelbaum, J., and Schlessinger, L.: Absorption of Vitamin A Through Human Skin, *Arch. Dermat. & Syph.* **46**:431 (Sept.) 1942.
4. Barwasser, N. C.: Keratosis Follicularis (Darier) Treated with Vitamin A, *Arch. Dermat. & Syph.* **44**:961 (Nov.) 1941.
5. Cannon, A. B.: Keratosis Follicularis, *Arch. Dermat. & Syph.* **44**:1163 (Dec.) 1941.
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7. Michelson, H. E.: Keratosis Follicularis (Darier's Disease), *Arch. Dermat. & Syph.* **45**:628 (March) 1942.
8. Abramowitz, E. W.: Darier's Disease, *Arch. Dermat. & Syph.* **45**:976 (May) 1942.
9. Peck, S. M.; Glick, A. W.; Sobotka, H., and Chargin, L.: Vitamin A Studies in Cases of Keratosis Follicularis (Darier's Disease), *Arch. Dermat. & Syph.* **48**:17 (July) 1943.
10. Newman, B. A.: Keratosis Follicularis (Darier) After Treatment with Vitamin A, *Arch. Dermat. & Syph.* **47**:288 and 293 (Feb.) 1943.
11. Carleton, A., and Steven, D.: Keratosis Follicularis: A Study of Four Cases, *Arch. Dermat. & Syph.* **48**:143 (Aug.) 1943.

and Leitner (1945)<sup>12</sup> and Leitner and Moore (1946)<sup>13</sup> in 1 out of 6 cases. Nevertheless, in spite of improvement following treatment with vitamin A in so many cases, it is clear that the disease is not a simple deficiency state; if it were, then deficiency, whether occurring naturally or experimentally, would reproduce the disease and treatment with adequate quantities of vitamin A would cure it. Laboratory tests might also be expected to produce evidence of deficiency. None of these three conditions is fulfilled, however. The state of the skin in naturally occurring deficiency, described by Loewenthal (1935),<sup>14</sup> Reiss (1936),<sup>15</sup> Frazier and Hu (1936)<sup>16</sup> and others, differs from that found in Darier's dyskeratosis. This is also true of experimentally produced deficiency, as recorded by Steffens, Bair and Sheard (1939).<sup>17</sup> Moreover, vitamin A, when given in large amounts and over long periods, seldom causes the cutaneous manifestations of Darier's disease to disappear entirely. So far as we are aware, the only patients reported as having recovered completely are the 2 in the cases described by Carleton and Steven (1943),<sup>11</sup> in which there was "complete involution with vitamin A therapy," and a case reported by Newman (1943).<sup>18</sup>

It must be remembered in estimating the effect of any form of treatment that the skin in Darier's dyskeratosis varies considerably from time to time, even when no treatment of any kind is being given. For instance, the patients in cases 3 and 4 both affirm that their skin is invariably worse in summer and that bright sunlight always has an adverse effect. Likewise, Swartz (1942)<sup>18</sup> and Hitch, Callaway and Moseley (1941)<sup>19</sup> mentioned that their patients got worse in summer, the latter

12. Leitner, Z. A., (a) in discussion on Stannus, H. C.: Vitamin A and the Skin, Proc. Roy. Soc. Med. **38**:337 (May) 1945; Brit. J. Dermat. **57**:209 (Nov.-Dec.) 1945; (b) Three Cases of Dyskeratosis Follicularis and Two Cases of Pityriasis Rubra Pilaris, *ibid.* **58**:11 (Jan.-Feb.) 1946.

13. Leitner, Z. A., and Moore, T.: Vitamin A in Darier's Disease, *Brit. J. Dermat.*, to be published.

14. Loewenthal, L. J. A.: The Manifestations of Vitamin A Deficiency in Man, *Ann. Trop. Med.* **29**:407 (Dec.) 1935.

15. Reiss, F.: Contribution to Cutaneous Manifestations of Vitamin A Deficiency, *Chinese M. J.* **50**:945 (July) 1936.

16. Frazier, C. N., and Hu, C. K.: Nature and Distribution According to Age of Cutaneous Manifestations of Vitamin A Deficiency: A Study of Two Hundred and Seven Cases, *Arch. Dermat. & Syph.* **33**:825 (May) 1936.

17. Steffens, L. F.; Bair, H. L., and Sheard, C.: Photometric Measurements on Visual Adaptation in Normal Adults on Diets Deficient in Vitamin A, *Proc. Staff Meet., Mayo Clin.* **14**:698 (Nov. 1) 1939.

18. Swartz, J. H.: Darier's Disease (Keratosis Follicularis), *Arch. Dermat. & Syph.* **45**:417 (Feb.) 1942.

19. Hitch, J. M.; Callaway, J. L., and Moseley, V.: Familial Darier's Disease (Keratosis Follicularis), *South. M. J.* **34**:578 (June) 1941.

calling special attention to the fact that the lesions were practically invisible during the winter. This is rather surprising, for relapses might be expected to occur when the vitamin A content of the diet is at its lowest, during the winter months, and indeed it is at this time that the symptoms of naturally occurring dietary deficiency have been found to be commonest. Again, the patients in cases 4 and 5 insisted that pregnancy was always accompanied with noted improvement in the condition of the skin. Hitch, Callaway and Moseley<sup>19</sup> reported that in their cases the skin became worse during menstruation.

Laboratory methods used to detect deficiency and to estimate the state of vitamin A nutrition are of two kinds: Firstly, the vitamin A and carotene levels in the plasma may be calculated, and, secondly, dark adaptation tests may be carried out.

Estimation of the vitamin A content in the blood has yielded conflicting results. For example, Peck, Glick, Sobotka and Chargin (1943)<sup>9</sup> found the plasma vitamin A level to be subnormal in 8 out of 10 cases and at the lower level of normal in the remaining 2. Moore (1946)<sup>20</sup> found the mean average level to be within normal limits in 3 cases, though individual estimation revealed subnormal levels in 2 of them on certain occasions. Carleton and Steven (1943),<sup>11</sup> however, reported normal levels in all their 4 cases, and Cornbleet, Popper and Steigmann (1944)<sup>21</sup> mentioned finding a normal level of plasma vitamin A in the only patient with Darier's dyskeratosis examined. In our own series the figures were within normal limits in all, including the 4 cases in which estimations were made before vitamin A therapy was begun. It must be remembered that determination of the plasma vitamin A content as a means of estimating the state of vitamin A nutrition is open to criticism (Carleton and Steven, 1943,<sup>11</sup> and Porter and Godding, 1945<sup>22</sup>).

A subnormal curve found by dark adaptation tests can provide satisfactory evidence of vitamin A deficiency only if the curve improves under vitamin A therapy. Of the 4 cases in our series in which dark adaptation tests were performed, the original curves (before vitamin A therapy was begun) were all outside the normal range as determined by Yudkin (1941).<sup>23</sup> After treatment there was a small but general tendency to improvement, the extent being indicated in the table; it will be seen,

20. Moore, T.: Plasma Vitamin A in Keratosis Follicularis and Pityriasis Rubra Pilaris, *Brit. J. Dermat.* **58**:17 (Jan.-Feb.) 1946.

21. Cornbleet, T.; Popper, H., and Steigmann, F.: Blood Vitamin A and Cutaneous Diseases, *Arch. Dermat. & Syph.* **49**:103 (Feb.) 1944.

22. Porter, A., and Godding, E. W.: (a) Dark Adaptation Studies in Patients with Diseases of the Skin, *Brit. M. J.* **1**:840 (June 16) 1945; (b) Pityriasis Rubra Pilaris and Vitamin A, *Brit. J. Dermat.* **57**:197 (Nov.-Dec.) 1945.

23. Yudkin, S.: A New Dark Adaptation Tester, *Brit. J. Ophth.* **25**:231 (May) 1941.

thought that this failure explains why large doses of vitamin A are required to produce the beneficial results which occur in many cases from treatment with vitamin A.

Whatever the defect may be, it appears to be inherited. Bettmann (1921)<sup>25</sup> called it "a specific or peculiar, inborn property of the skin in Darier's disease which responds to trauma of all kinds in a way specifically characteristic of this disease." The nature of the inheritance, however, is still under discussion. According to F. Fischer (1925)<sup>26</sup> it is a highly irregular dominant, whereas Cockayne (1933),<sup>27</sup> after reviewing the family histories in more than 200 cases, suggested that, as far as the familial cases are concerned, the defect is a simple dominant and that in isolated cases "the abnormality arose in each case *de novo* by mutation." It is because of this difference of opinions that we give details of siblings in the notes on the cases.

The foregoing explanation of the sometimes beneficial effect of vitamin A in cases of Darier's dyskeratosis is based on the histologic changes of the disease. It is as yet uncertain whether these changes are associated with impairment of hepatic function or abnormalities in the balance of vitamin A between the hepatic reserves and blood plasma, as suggested by Leitner and Moore (1946).<sup>13</sup> This question requires further investigation.

One fact is, however, perhaps worth mentioning. Apart from phrynoderma—the naturally or experimentally occurring deficiency which can be cured by adequate dosage—vitamin A has been tried in numerous cutaneous diseases, particularly in Darier's disease, in pityriasis rubra pilaris (Gross, 1941<sup>28</sup>; Brunsting and Sheard, 1941<sup>29</sup>; Weiner and Levin, 1943<sup>30</sup>; Porter and Godding, 1945,<sup>22</sup> and Leitner, 1945<sup>12</sup>) and in ichthyosis (Peck, Glick and Chargin, 1943<sup>31</sup>). In Darier's dyskeratosis and in pityriasis rubra pilaris the effect is sometimes good. In contrast to this is the response in 2 cases of ichthyosis reported by Peck, Glick and Chargin (1943).<sup>31</sup> In both, the plasma vitamin A content was greatly below normal and dark adaptation tests gave subnormal values; yet no improvement was produced by vitamin A even when the vitamin blood levels were brought back to normal and maintained so for

27. Cockayne, E. A.: *Inherited Abnormalities of the Skin and Its Appendages*, London, Oxford University Press, 1933.

28. Gross, P.: *Pityriasis Rubra Pilaris and Vitamin Therapy*, Arch. Dermat. & Syph. **44**:270 (Aug.) 1941.

29. Brunsting, L. A., and Sheard, C.: *Dark Adaptation in Pityriasis Rubra Pilaris*, Arch. Dermat. & Syph. **43**:42 (Jan.) 1941.

30. Weiner, A. L., and Levin, A. A.: *Pityriasis Rubra Pilaris of Familial Type: Experience in Therapy with Carotene and Vitamin A*, Arch. Dermat. & Syph. **48**:288 (Sept.) 1943.

31. Peck, S. M.; Glick, A. W., and Chargin, L.: *Vitamin A Studies in Cases of Ichthyosis*, Arch. Dermat. & Syph. **48**:32 (July) 1943.

a long time. In ichthyosis there are no major changes in the basal cells resembling those which occur more or less regularly in Darier's disease and to a lesser degree in pityriasis rubra pilaris. Havas, quoted by Juliusberg (1931),<sup>32</sup> reported increase in number of the basal cells and loss of prickles in pityriasis rubra pilaris. It seems to be no mere coincidence that in Darier's dyskeratosis and pityriasis rubra pilaris, the two diseases which have certain histologic features in common, response to vitamin A therapy is sometimes excellent whereas in the aforementioned cases of ichthyosis, in which the histologic structure is totally different, no benefit from treatment with vitamin A was obtained.

The term "keratosis follicularis" has been avoided throughout this paper because it is doubtful whether the keratosis occurring in Darier's disease is principally one of the follicles (Darier, 1889<sup>1</sup>; Brunauer, 1931,<sup>25</sup> and Ellis, 1944<sup>33</sup>). It is for this reason that we prefer the synonyms "Darier's disease" and "Darier's dyskeratosis."

#### SUMMARY

The vitamin A and carotene levels in the plasma were within normal limits in 4 cases of Darier's disease in which estimations were made before treatment was begun.

Dark adaptation tests carried out before vitamin A was given in 4 cases revealed curves somewhat outside the normal range in all, with improvement under treatment in 3, although close correlation with the clinical picture was not established.

Of 7 cases, great clinical improvement with vitamin A therapy occurred in 1, much in another, but little in 3 and none in 2.

It is suggested that doses of about 100,000 units of vitamin A should be given daily and continued until improvement ceases, when smaller doses may be instituted. Treatment should not be abandoned under two months at least.

No benefit was obtained from inunction of an ointment containing 5,000 international units of vitamin A per gram.

The histopathologic changes of Darier's disease show as fundamental features hyperplasia of the basal cells of the epidermis and loss of prickles. As a consequence of these changes, fissures and lacunas, *corps ronds* and "grains" appear and the primary functions of the basal cells, keratinization and pigment formation, are grossly disturbed. It is suggested that another function of the basal cells is more or less upset in Darier's disease, namely, the ability to utilize vitamin A or its derivatives in a normal manner or to synthesize vitamin A-containing com-

32. Juliusberg, F.: Pityriasis rubra pilaris, in Jadassohn, J.: Handbuch der Haut- und Geschlechtskrankheiten, Berlin, Julius Springer, 1931, vol. 7, pt. 2, p. 144.

33. Ellis, F. A.: Keratosis Follicularis Is Not Primarily a Follicular Disease, Arch. Dermat. & Syph. 50:27 (July) 1944.

pounds as required. This failure may explain why large doses of vitamin A are required to produce the beneficial effect which occurs in many cases from treatment with vitamin A.

We believe that support is given to this hypothesis by the good results of treatment with vitamin A in pityriasis rubra pilaris, a disease in which the histologic picture resembles in certain respects that seen in Darier's disease.

The fact that in 2 cases of ichthyosis in which evidence of vitamin A deficiency was reported by Peck, Glick and Chargin no benefit was obtained by vitamin A therapy seems to favor the foregoing hypothesis.

Prof J. R. Marrack, M.D., D.S.O., M.C., estimated the levels of vitamin A in the plasma in all cases; Dr. Sydney Thompson and Dr. H. Corsi referred cases to us for investigation, and Messrs. Crookes Laboratories, Ltd., loaned the apparatus for dark adaptation tests and generously supplied vitamin A.

deformed and poorly stained. Levaditi and Po suggested that irradiated ergosterol was worthy of trial in the treatment of human tuberculosis.

Fanielle<sup>4</sup> followed this line of investigation, using irradiated ergosterol in the treatment of human tuberculosis and after twelve years of observations concluded that it was of distinct value. During the later years of his observations he used 15 mg. of vitamin D<sub>2</sub> daily for fifteen days along with calcium gluconate. Under this regimen he reported favorable results in 4 cases of lupus vulgaris, 2 cases of ulcerated tuberculosis and 1 case of verrucous cutaneous tuberculosis. Alechinsky<sup>5</sup> confirmed these observations and reported the cure in several cases by the same method.

In 1943 and 1944 Charpy<sup>6</sup> reported 39 cases of lupus vulgaris in which treatment was by the same method except that vitamin D was administered in an alcoholic solution, less frequently and over a longer period. Cures were obtained in each instance, although in 27 cases some form of local destructive therapy was used in addition to the vitamin and calcium. According to Charpy the results were rapid and dramatic, and the beneficial effect, greatest during the initial period, continued for four or five months. The mucosal lesions, lymphangitis and adenitis were quickly reduced, but the cutaneous nodules were more resistant and often required cauterization.

Adopting the method which was described by Charpy, Gougerot and Gaullier<sup>7</sup> obtained cures in about 60 per cent of 32 patients with lupus vulgaris. Huriez and Leborgne<sup>8</sup> reported 4 failures out of 15 cases of lupus vulgaris and satisfactory results in 2 cases of lichen scrofulosus and 1 case each of tuberculous gumma and erythema induratum. Garric<sup>9</sup> obtained remarkable results in 10 cases of lupus vulgaris in which treatment was by Charpy's method. In 2 cases of particularly severe lupus vulgaris rapid cure was obtained by the intramuscular

4. Fanielle, M. G.: Le traitement des affections d'origine tuberculeuse par l'ergosterol irradié associé à la calcithérapie, *Scalpel* **95**:539 (Dec.) 1942.

5. Alechinsky, A.: La méthode de Fanielle dans le traitement des tuberculoses cutanées, *Bruxelles-méd.* **25**:838 (Sept. 23) 1945.

6. Charpy, M. J.: Technique de traitement du lupus tuberculeux, *Ann. de dermat. et syph.* **3**:331 (Nov.-Dec.) 1943; Les réactions tuberculiniques après traitement des lupus tuberculeux, *ibid.* **4**:110 (March-April) 1944; Le traitement des lupus tuberculeux et tuberculoses cutanées par la vitamine D, *Bull. Acad. de méd., Paris* **108**:498 (Oct.) 1944.

7. Gougerot, H., and Gaullier: Traitement de Charpy dans les tuberculoses cutanées, *Ann. de dermat. et syph.* **4**:210 (July-Aug.) 1944.

8. Huriez, C., and Leborgne, J.: Action de la vitamine D à doses massives dans le traitement des tuberculoses cutanées, *Ann. de dermat. et syph.* **4**:211 (July-Aug.) 1944.

9. Garric, M.: A propos de traitement du lupus tuberculeux par la méthode de Charpy, *Ann. de dermat. et syph.* **4**:313 (Nov.-Dec.) 1944.

injection of vitamin D ("sterogyl") in oil. Bureau and Barrière<sup>10</sup> treated 26 patients with cutaneous tuberculosis by the same method and were able to cure all but 1 (a case of papulonecrotic tuberculid which seemed to be made worse by the therapy). Vachon<sup>11</sup> treated 29 patients with only 1 failure, although he resorted to local therapy to complete the cure in most cases. Michel and Pellerat<sup>12</sup> also reported favorably on the method.

From the Finsen Institute, Meyer, Gaulier and Desgrez<sup>13</sup> reported the treatment of over 300 patients by Charpy's method. Good results were obtained in about 75 per cent, but a high incidence of recurrence was reported.

Dowling and Thomas<sup>14</sup> treated 38 patients with lupus vulgaris by oral administration of 150,000 units of calciferol (vitamin D<sub>2</sub>) daily. The results of treatment were assessed in 32 patients, 18 of whom appeared to be cured and 9 considerably improved.

A recent issue of the *Annales de dermatologie et de syphiligraphie*<sup>15</sup> contained a symposium on this subject with a complete bibliography.

#### RÉSUMÉ OF CASES

We have administered vitamin D to 6 patients with cutaneous tuberculosis. They have been under observation for periods varying from two to five months. The small number of patients and the short period of observation make this no more than a preliminary report. Two patients with lupus vulgaris, 1 with tuberculosis colliquativa and

10. Bureau, Y., and Barrière: Résultats obtenus par la vitamine D<sub>2</sub> (méthode de Charpy) dans le traitement de la tuberculose cutanée et de certaines dermatoses, Ann. de dermat. et syph. 5:196 (July-Aug.) 1945.

11. Vachon, R.: Le traitement du lupus tuberculeux par la méthode de Charpy, Ann. de dermat. et syph. 6:91 (Feb.) 1946.

12. Michel, P. J., and Pellerat, J.: Résultats éloignés de la méthode de Charpy pour le traitement des lupus, Ann. de dermat. et syph. 4:114 (March-April) 1944.

13. Meyer, J.; Gaulier, and Desgrez: La vitamine—calcithérapie dans le traitement du lupus au laboratoire du Finsen, Ann. de dermat. et syph. 6:348 (May) 1946.

14. Dowling, G. G., and Thomas, E. W. P.: Treatment of Lupus Vulgaris with Calciferol, Brit. J. Dermat. 58:45 (March-April) 1946.

15. Charpy, M. J.: Le traitement des tuberculoses cutanées par la vitamine D<sub>2</sub> à hautes doses, Ann. de dermat. et syph. 6:310 (May-June) 1946. Fanielle, M. G.: Entretien sur la question de priorité, ibid. 6:346 (May-June) 1946; Toxicité de la méthode, ibid. 6:347 (May-June) 1946. Meyer, J.; Gaulier, and Desgrez: La vitamine-calcithérapie dans le traitement du lupus au laboratoire du Finsen, ibid. 6:348 (May-June) 1946. Lapière, S.: Résultats du traitement du lupus vulgaire par les vitamines D à hautes doses, ibid. 6:350 (May-June) 1946. Lefèvre, P., and Hallé, G.: 35 cas de lupus tuberculeux traités par la vitamine D<sub>2</sub> à haute dose (traitement de Charpy): Remarquables résultats, ibid. 6:355 (May-June) 1946. Levaditi, M. C.: Action calcifiante de la vitamine D sur les lésions tuberculeuses expérimentales, ibid. 6:356 (May-June) 1946.

3 with erythema induratum were included in the study. All, with the exception of 1 case of tuberculosis colliquativa, were old cases which had resisted previous therapy. The results were less dramatic than had been expected from a study of the French reports, but each patient has shown an initial and progressive improvement. None are as yet cured.

As the alcoholic solution which was recommended by Charpy was not commercially available in the United States, viosterol in oil was used in a dosage of 150,000 international units daily. An adequate intake of calcium was assured by having the patients drink at least 1 quart (946 cc.) of milk daily.

#### TOXIC REACTIONS

Most drugs, including vitamin D, have a limit of dosage which if exceeded results in toxic and occasionally fatal reactions. The extreme toxicity of viosterol as described in the older reports was probably due to the presence of an excess of toxisterol.<sup>16</sup> In human beings and with modern methods of preparation, the incidence of intoxication is relatively low, and the toxic dose is about 20,000 international units per kilogram of body weight per day.<sup>17</sup> This is from five to ten times greater than the doses that were employed in the present study. The kidneys and the aorta are parts of the body which are most vulnerable to excessive doses, and, according to some, renal disease and arteriosclerosis constitute contraindications to such therapy.

Thatcher<sup>18</sup> called attention to the possibility, especially in infants, of an idiosyncrasy to viosterol and reported a case in which this intolerance may have been the cause of death.

For the most part, administration of vitamin D in the doses which are recommended is perfectly safe, and the French authors comment on the lack of reactions. Dowling and Thomas<sup>14</sup> noted signs of intolerance in 8 out of 38 patients (mild in all but 1), all of whom were able to tolerate smaller doses without discomfort.

In 1 patient who was observed by us, anorexia and loss of weight occurred but were of such mild degree that we were able to continue treatment with full dosage.

The symptoms of overdosage as listed by Bills<sup>16</sup> are: nausea and loss of appetite, vomiting, cramps, diarrhea and frequent urination, occasionally neuralgia along the course of the mandibular nerve, tenderness of the gums and teeth, muscular and articular pains, dizziness,

16. Bills, C. E.: Physiology of the Sterols, Including Vitamin D, *Physiol. Rev.* **15**:1 (Jan.) 1935.

17. Steck, I. E.; Deutsch, H.; Reed, C. I., and Struck, H. C.: Further Studies on Intoxication with Vitamin D, *Ann. Int. Med.* **10**:951 (Jan.) 1937.

18. Thatcher, L.: Hypervitaminosis D, *Lancet* **1**:20 (Jan. 4) 1936.

The means by which irradiated ergosterol (vitamin D<sub>2</sub>) exerts a beneficial influence on cutaneous tuberculosis is not definitely known. Large doses may have an action quite different from the physiologic effects of small antirachitic doses. The substance may be acting as a drug rather than as a vitamin, as the sterols themselves have a detoxifying action against numerous hemolytic agents, venoms and bacterial toxins.<sup>16</sup> Levaditi and Li<sup>3</sup> observed that tuberculous tissue in animals had a selective affinity for calcification and that the administration of large doses of irradiated ergosterol aided this process. They expressed the opinion that this calcification interfered with the propagation of the tubercle bacilli and prevented their spread to adjacent areas. If the beneficial effect of irradiated ergosterol is due entirely to such selective calcification, it is possible that tachysterol, which is present in irradiated ergosterol and which has no antirachitic activity, may be the substance which is responsible for the therapeutic effect.

The method of Charpy produced remarkable clinical results in lupus vulgaris according to Vachon and Feroldi,<sup>22</sup> but histologic evidence of cure was not always obtained. In most cases they observed a progressive cicatricial smothering of the lesions with disappearance of the active inflammatory elements. They stated the belief that the improvement was not due to actual calcification of the lesions.

Crimm and Strayer<sup>23</sup> expressed the belief that the administration of large doses of viosterol to patients with pulmonary tuberculosis was attended by more rapid clearing and fibrosis in some cases. They concluded that this was the result of an increase in the nondiffusible calcium which was produced by the hypervitaminosis. Gelfan<sup>24</sup> showed that the consumption of oxygen of an isolated tissue (frog muscle) was increased during the administration of viosterol. Reed, Thacker, Dillman and Welch<sup>25</sup> observed that the administration of large doses of vitamin D increased the metabolic rate, and if continued a cellular injury and later a deposit of calcium in the injured cells resulted.

In lupus vulgaris there exists a delicate but fixed balance between the invading organism and the bodily resistance, neither being able to advance or retreat except over periods of months or years. Healing does

22. Vachon, R., and Feroldi, J.: Le traitement du lupus tuberculeux par la méthode de Charpy: Les résultats anatomiques, Ann. de dermat. et syph. **5**:241 (Sept.-Oct.) 1945.

23. Crimm, P. D., and Strayer, J. W.: Vitamin Therapy in Pulmonary Tuberculosis, Am. J. M. Sc. **187**:557 (April) 1934. Crimm, P. D.: Vitamin Therapy in Pulmonary Tuberculosis, Am. Rev. Tuberc. **26**:112 (Aug.) 1932.

24. Gelfan, S.: The Effect of Viosterol upon the Oxygen Consumption of Frog's Muscle, Am. J. Physiol. **113**:464 (Oct.) 1935.

25. Reed, C. I.; Thacker, E. A.; Dillman, L. M., and Welch, J. W.: The Effect of Irradiated Ergosterol on the Metabolism of Normal Dogs, J. Nutrition **6**:355 (July) 1933.

## SUMMARY

The literature concerning the use of vitamin D in cutaneous tuberculosis is reviewed.

A modification of the methods suggested by Fanielle and Charpy was used in 6 cases. At the time of this report all patients were considerably benefited, but insufficient time has elapsed to draw any final conclusions.

The use of propylene glycol as a vehicle for viosterol is suggested.

The experimental evidence concerning selective calcification, increased cellular metabolism and injury is reviewed, and a possible explanation is offered for the effect of therapy with massive doses of vitamin D in human tuberculosis.

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contact dermatitis of the face, hands and fingers after handling penicillin solution. His reaction to a patch test with penicillin was positive.

Silvers<sup>3</sup> patient, a chemist, experienced contact dermatitis of the eyelids and of the penis from handling yellow amorphous sodium penicillin. Reactions to patch tests with this substance were positive, but reactions were negative with pure white crystalline sodium penicillin solution.

Barker<sup>4</sup> reported a similar positive reaction to a patch test in a physician handling penicillin.

Pyle and Rattner<sup>5</sup> in a patch test of a patient, a physician who had contact dermatitis from penicillin noted that the patient reacted negatively to the culture medium, mildly to pure penicillin and to crystalline penicillin and strongly to the whole product. They concluded that the dermatitis was from penicillin itself. Three corpsmen who handled penicillin had pruritus of the face and of the genitals without actual dermatitis.

Siefert<sup>6</sup> reported severe contact dermatitis of the thighs and of the knees from the use of a wet dressing of penicillin in the treatment of secondarily infected tinea cruris. Presumably the tissues had been sensitized by the fungous infection of the groin. Reaction to a patch test was positive.

Pringle<sup>7</sup> said, "I do not have exact figures, but there is approximately a 20 per cent incidence of dermatitis resulting from the local application of penicillin, particularly on the face (when used for sycosis vulgaris or similar diseases). This is irrespective of previous use parenterally, orally or by local application. The percentage of dermatitis is considerably less when used on areas other than the face. The base used (in my experience) does not seem to make any difference. I believe that the brand does make some difference, but because of the process of manufacture of the ointment I have used I have had no real check on this. The dermatitis from penicillin resembles the dermatitis seen in ammoniated mercury sensitivity. I recommend to all patients using the ointment that they employ a patch test for two or three days before applying it to larger areas."

3. Silvers, S. H.: Contact Dermatitis From Amorphus Sodium Penicillin, Arch. Dermat. & Syph. **50**:328-329 (Nov.) 1944.

4. Barker, A. N.: Allergic Reactions to Penicillin, Lancet **1**:177-178 (Feb. 10) 1945.

5. Pyle, H. D., and Rattner, H.: Contact Dermatitis from Penicillin, J. A. M. A. **125**:903 (July 29) 1944.

6. Siefert, H. J.: Personal communication to the authors.

7. Pringle, B.: Personal communication to the authors.

Markson,<sup>8</sup> Bechet<sup>9</sup> and Bedford<sup>10</sup> have reported examples of contact dermatitis from penicillin, patch tests with which also showed positive reactions.

We have seen cases of contact dermatitis from penicillin in our own practice. A physician experienced severe dermatitis of the face when he used a solution containing 500 units of penicillin per cubic centimeter for folliculitis of the beard. Reaction to a patch test was mildly positive. We have had 12 more patients with contact dermatitis from penicillin, all of whom were being treated for various dermatoses. We do not have knowledge of the source of manufacture. In 6 of these patients the dermatitis resulted from the use of penicillin in ointment form. Six patients used penicillin in solution form as continuous wet compresses in dilution of 100,000 units to a pint of water.

#### CONTACT CHEILITIS, STOMATITIS AND CONJUNCTIVITIS

Goldman<sup>11</sup> reported severe cheilitis in a patient who had used sodium penicillin solution and who had previously used a calcium penicillin ointment for aphthous stomatitis without reaction. Reactions to patch tests with the offending solution were positive but were negative with each of three other brands of sodium penicillin solution and with calcium penicillin ointment. These observations are of practical importance, as they indicate that we may be able to continue needed penicillin therapy in patients who are sensitive to penicillin by changing the brand of penicillin.

Wright and Rule<sup>12</sup> reported mild to severe stomatitis, glossitis or pharyngitis in 16 of 151 patients who were given sodium penicillin lozenges or calcium penicillin lozenges for various dental and oral infections. They do not make mention of patch tests.

Phillips<sup>13</sup> reported 17 instances (up to 18 per cent of his cases) of mild to severe glossitis and stomatitis due to penicillin lozenges and penicillin troches. These contained calcium penicillin, powdered sugar, calcium stearate and acacia. Since all of the ingredients, other than penicillin, are in common use in lozenges the author concluded that calcium penicillin was the irritant.

8. Markson, L. S.: Dermatitis Venenata Following Use of Penicillin Ointment, *Arch. Dermat. & Syph.* **52**:384 (Nov.-Dec.) 1945

9. Bechet, P. E.: Induced Sensitivity from the Topical Use of the Sulphonamides and Penicillin, *Pennsylvania M. J.* **49**:417-420 (Jan.) 1946.

10. Bedford, P. D.: A Case of Penicillin Dermatitis, *Brit. M. J.* **1**:51-52 (Jan. 12) 1946.

11. Goldman, L.: Cheilitis from Local Use of Penicillin Solutions in the Mouth: Report of Cases, *Arch. Dermat. & Syph.* **53**:133-134 (Feb.) 1946.

12. Wright, R. B., and Rule, R. W., Jr.: *J. California State Dent. A.* **21**:177 (Nov.-Dec.) 1945; **22**:7 (Jan.-Feb.) 1946.

13. Phillips, E.: Glossitis and Stomatitis Due to Penicillin Lozenges and Troches, *Permanente Found. M. Bull.* **4**:20-23 (Feb.) 1946.

Pringle<sup>7</sup> noted a 10 per cent incidence of stomatitis from the use of troches containing penicillin.

We have seen 2 cases of conjunctivitis and dermatitis of the eyelids after use of eye drops containing penicillin. Several ophthalmologists have reported similar cases to us. Pringle reported a 1 per cent incidence of conjunctivitis and dermatitis of the eyelids among users of drops and ointments for the eye containing penicillin. Benkwith<sup>14</sup> noted positive reactions to intradermal tests and to patch tests in a patient who experienced dermatitis of the eyelids and of the face after instillation of calcium penicillin solution into the conjunctival sacs.

#### DERMAL TYPES OF REACTIONS

Toxic macular or scarlatiniform eruptions which follow the injection of penicillin are fairly common. They generally occur within the first few days after injections of penicillin, which is earlier than the onset of urticaria after administration of penicillin. We have not seen any of these eruptions progress to generalized exfoliative dermatitis, nor have we heard of any such cases in the practices of our colleagues.

The commonest dermal reaction is urticaria. There have been many reports in literature of its occurrence.<sup>15</sup> Lyons<sup>15b</sup> has reported an incidence of urticaria of 15.7 per cent among 209 patients after injection of penicillin. So many of our colleagues reported examples of urticaria among their patients that we ceased recording the details, as they all followed a rather typical pattern. Urticaria usually occurred on about the seventh, eighth or ninth day after injection of penicillin and varied from a mild form to one with such severe involvement that 1 of our patients threatened suicide. Two of our patients have had severe urticaria associated with nausea, fever and painful swollen joints of the type seen in typical serum sickness. Dr. F. G. Novy Jr. permitted us to see 1 of his patients with this type of severe reaction. Three physicians known to us have suffered from severe urticaria after injections of penicillin. There has not been any uniformity in the type of penicillin injected into these patients with urticaria, various brands, salts and vehicles having been employed.

One patient whom we saw at the Alameda County Hospital had macules, papules and painful nodules of the erythema multiforme-

14. Benkwith, K. B.: Allergy to Penicillin Calcium Topically in Blepharconjunctivitis, U. S. Nav. M. Bull. **46**:279-280 (Feb.) 1946.

15. (a) Macey, H. B., and Hays, T. G.: Allergic Reactions to Penicillin Therapy: Report of Cases, U. S. Nav. M. Bull. **45**:1143-1146 (Dec.) 1945. (b) Lyons, C.: Penicillin Therapy of Surgical Infections in U. S. Army, J. A. M. A. **123**:1007-1018 (Dec. 18) 1943. (c) Crisp, L. H.: Allergy to Penicillin, ibid. **126**:429-430 (Oct. 14) 1944.

Krause<sup>21</sup> has treated 5 patients who experienced industrial contact dermatitis of the hands during the process of manufacture of penicillin. In 1 patient employed in the grinding and bottling department dermatitis of the face, arms and neck developed immediately after the first day of contact with penicillin. This patient had not previously used penicillin. Reactions to patch tests with dry penicillin and with solutions of penicillin were positive. In 4 patients in the processing department dermatitis of the face, hands, wrists or arms developed within three days to three weeks after beginning work with penicillin. All showed strongly positive reactions to patch tests with penicillin solutions.

#### COMBINED DERMAL AND EPIDERMAL SENSITIZATION

One of us (H. J. T.)<sup>22</sup> discussed combined sensitization of the epidermis and the dermis to the sulfonamide drugs and showed that application of these drugs to the skin could produce contact dermatitis, which, in turn, sensitized the whole organism, so that the patients exhibited dermal reactions in the form of urticaria or toxic erythema when the drug was given by mouth. We observed that this can happen also from the application of penicillin to the skin. We were treating 1 of our colleagues for folliculitis and dermatitis of the beard and prescribed a penicillin solution containing 500 units per cubic centimeter. Within twelve hours there was a violent exacerbation of the dermatitis of the face. This subsided in about a week, at which time a patch test elicited a mildly positive reaction. The dermatitis of the face had disappeared entirely when, two months later, he was given an intramuscular injection of penicillin for a dental infection. This was followed within twelve hours by a severe recurrence of the dermatitis of the face. Within another day a generalized pruritic erythematous urticarial eruption had developed.

A similar case was reported by Kolodny and Denhoff.<sup>23</sup> Their patient suffered an exacerbation of dermatitis of the hand when penicillin ointment was first applied. Twenty-five days later he was given 20,000 units intramuscularly every three hours. After the third injection a generalized erythematous eruption developed. The healing lesions of the preexisting dermatitis of the hand became hyperemic, pruritic, vesicular and wet. Five days later another course of injections of penicillin, of another brand, produced the same types of reactions, and three days later generalized urticaria developed.

In their investigations Kolodny and Denhoff noted that there was a much higher incidence of immediate reactions (25 per cent) to injec-

21. Krause, M.: Personal communication to the authors.

22. Templeton, H. J.: Epidermal and Dermal Sensitization (Co-Existing in the Same Individual), *J. A. M. A.* **127**:908-911 (April 7) 1945.

23. Kolodny, M. H., and Denhoff, E.: Reactions in Penicillin Therapy, *J. A. M. A.* **130**:1058-1061 (April 20) 1946.

**EXPERIMENT 2.**—Serums from 5 persons with urticarial reactions were injected intradermally into 7 of our office staff. Forty-eight hours later patch tests of an isotonic solution of sodium chloride containing 1,000 units of sodium penicillin per cubic centimeter were applied to the areas where the serums were injected and were observed daily for a week. Reactions were not seen. This could mean one of two things: first, that there were no circulating antibodies in the serums from those with urticarial reactions, or, second, that there was insufficient trans-epidermal penetration of the solution of penicillin in the patch test. Because of results in the next experiment we favor the second of these explanations.

**EXPERIMENT 3.**—The serums from the 5 persons with reactions were injected intradermally into 7 of our office staff. Forty-eight hours later an isotonic solution of sodium chloride containing 1,000 units of sodium penicillin per cubic centimeter was scratched into the areas injected with the serums. Reading at the end of twenty minutes showed 1 plus to 2 plus reactions on the basis of a 1 plus to 4 plus scale as compared with negative reactions in 4 of our staff used as controls. We regarded this as evidence of the presence of circulating antibodies.

#### CONTROL OF REACTIONS

Cutaneous reactions to penicillin may be lowered in incidence by a knowledge of the danger of penicillin and by a proper selection of cases.

Patients whose skins are in unstable equilibrium because of some exudative dermatoses are poor risks with penicillin either topically applied or injected. If there is present an added secondary pyogenic infection, penicillin may be tried cautiously. If improvement does not occur in three to five days penicillin should probably be discontinued, as longer periods of use are more apt to sensitize the patient. It is permissible to use penicillin topically in simple pyoderma or in impetigo, as it usually effects cures in these diseases in the safe period of the first week, before sensitization is likely to occur.

There is some evidence that a change of brand or of vehicle may prevent further reactions in a patient sensitive to penicillin, but this has not been the experience of most investigators.

The newer antihistamine drugs such as "benadryl hydrochloride" N.N.R. (diphenhydramine hydrochloride) or "pyribenzamine hydrochloride" N.N.R. (tripelennamine hydrochloride) may be found to be of value in preventing or in alleviating urticaria from penicillin.

#### CONCLUSIONS

1. Penicillin given by topical application, by oral ingestion or by injection sensitizes a certain percentage of persons.
2. The reactions most frequently seen are contact dermatitis and urticaria. Other reactions occur.
3. Patch tests, scratch tests, intradermal tests and passive transfer each give varying reactions in patients sensitive to penicillin.

However, I wanted to talk about the results obtained by my colleagues and me at Barnard Free Skin and Cancer Hospital and Washington University, which were published in the March and April 1946 issues of the ARCHIVES OF DERMATOLOGY AND SYPHILOLOGY. Significant statements are contained therein about persons who handle penicillin. Seven workers in a pharmaceutic plant handled the drug, and all 7 gave positive reactions to patch tests when penicillin was applied. They gave negative reactions to patch tests with an acetone extract of the fungus itself. On injecting penicillin into these patients parenterally reaction was not obtained, nor was there any flare-up at the point where previously there had been a positive reaction to a patch test.

We ran a series of patch tests on 200 persons (surgical patients, workers in hospitals and workers in factories). By using the menstruum and the extract of the organism as controls, we found that 4.5 per cent gave positive reactions. We were able to retest some of the subjects who had given a negative reaction ten days to two weeks later. Seventeen of the 60 or 70 subjects whom we retested showed positive reactions. Therefore, we feel that by means of the patch test we were able to produce epidermal sensitivity. Our experiments did not indicate that epidermal sensitivity always is accompanied by vascular sensitivity. Although this possibly can occur, apparently it does not occur often.

I am grateful for having had the opportunity to listen to Dr. Templeton's paper and for the information which he has added to what had already been known and reported.

DR. PAUL E. BECHET, Elizabeth, N. J.: Dr. Templeton and his collaborators are to be congratulated on a timely and valuable contribution. In a recent paper I said that the incidence of sensitization from the local use of penicillin was rare, but I qualified this statement by saying that this rarity might be due to the fact that the drug had been in use only recently and that sufficient time had not elapsed to permit evaluation of attendant accidents. Yet even at this early period Pyle and Rattner, also Binkley and Brockmole, had reported a few cases. I also had observed 2 cases in private practice.

Since January 1946 the incidence of dermatitis after the local use of penicillin has, in my experience, tremendously increased. It is apparently a new medical hazard, as many of the cases observed occurred among physicians and among laboratory workers engaged in the manufacture of penicillin. In the past few months I have seen a dozen or more private patients with severe dermatitis which appeared after local use of the drug. Induced sensitivity from topical use of penicillin occurred in a few patients. In 2 instances the drug had been used for several weeks without any untoward effects; yet weeks after it had been discontinued the same preparation used for relief of a recurrence resulted in severe dermatitis within forty-eight hours.

Penicillin is now being used locally more and more by general practitioners, who have been wrongly assured of complete lack of local reaction by both manufacturers and enthusiasts. In my opinion, the frequency of dermatitis from local use of penicillin will in the near future equal if not exceed the occurrence of dermatitis from the local use of sulfonamide compounds.

DR. UDO J. WILE, Ann Arbor, Mich.: I was glad to hear Dr. Templeton refer to the delayed reactions to penicillin. Short of the few cases of fatal outcome after penicillin therapy, the most serious manifestations I have noted are of edema involving the larynx and the lungs.

The first case that was brought to my attention occurred in a man who had received 2,400,000 units of penicillin. He had remained well and had not had

difficulty during his stay in the hospital. Five days after his discharge he experienced giant urticaria which soon involved the mucous membranes of his mouth. Then laryngeal edema and pulmonary edema developed. Only with difficulty was he assisted to breathe, and for a time it looked as though he might die.

Shortly after his recovery, within two days, he had a relapse, a milder attack of the same thing.

That sort of reaction has been encountered seldom but often enough to indicate that it might be a definite reaction to penicillin. Close to it is the reaction which Dr. Templeton has referred to as a serum-sickness-like reaction, in which, besides general edema and urticaria there is arthritic pain, and occasionally a tendency for hydrops to occur in the joints.

I can recall at least 6 cases of exfoliative dermatitis after administration of penicillin. All, however, were mild and in no way comparable to the exfoliative dermatitis due to arsenic. I dare say that I could tell you of hundreds of cases of exacerbation of Trichophyton infections of the feet in patients who were admitted and treated for syphilis with penicillin. Some of these Trichophyton infections were apparently quiescent and were not noticed on admission. In some instances the eruptions of bullae, erosions and interdigital lesions were so severe that the patients required special treatment for that infection during their stay. So, apparently penicillin does cause exacerbation of ordinary Trichophyton infections of the feet.

DR. HERBERT RATTNER, Chicago: I think that Pyle and I were the first to report a case of contact dermatitis from penicillin. It occurred in an army physician who was administering penicillin to patients. At the time we were able with difficulty to obtain some crystalline penicillin for a patch test. In this case we obtained strongly positive reactions from crystalline penicillin and from the whole penicillin product that the physician was using. The liquor medium did not produce a reaction and, therefore, we concluded that in this case the dermatitis was due to sensitivity to the penicillin itself.

We have also observed 4 cases of severe serum sickness type of reaction and a number of cases of urticaria. The reactions seemed to occur in waves. The cases were more numerous just after penicillin was released for civilian use, and since then there seem to have been waves of reactions as though the various stocks of the drug may have played a causative role.

The urticarial type of reaction has generally responded well to treatment with "benadryl hydrochloride" N.N.R. (diphenhydramine hydrochloride), but the serum sickness type has not. Until today it was my impression that penicillin could be administered freely and that the danger from its use was overstressed. Pyle and I had not seen any renal block, and there were not any hemopoietic changes, cerebral reactions or other dangerous reactions reported from the use of penicillin. The drug is an eminently useful one, but the report today of 2 fatal reactions from its use changes the picture.

DR. E. WILLIAM ABRAMOWITZ, New York: I can confirm the observations of Dr. Templeton. To the reactions hitherto reported I would like to add herpes simplex of the face after the use of penicillin for osteomyelitis.

The introduction of new drugs invariably brings in its wake a host of new reactions. In fact, one is almost led to believe that if a drug is going to be of any value, it is bound to produce untoward effects in someone.

Sensitivity to penicillin presents some difficulties not present in cases in which simple chemical drugs are used. We know now that penicillins G, X, F and K are identifiable from one another in the side groups attached to a common nuclear

structure. Commercial penicillin shows differences in the relative proportion of those fractions and in the degree of purity, which seem to have bearing on the antibiotic action of the drug. It may be that sensitivity varies with the individual components of penicillin, the relative proportion of each, or the synergistic effects of the various fractions in combination. Furthermore, the culture medium and the vehicle used in topical application have to be considered also. Another point that I think we need to stress is that penicillin has a photosensitizing action, for eruptions from the drug seem to favor the areas that are exposed to the sun.

In addition to the sensitization that develops in patients receiving penicillin, there is an increasing number of workers, nurses and physicians handling penicillin who experience dermatitis. In Dr. Rosen's service at the Skin and Cancer Unit 3 of my associates and I became sensitized through the handling of penicillin. An annoying dermatitis of the face develops, precluding the handling of penicillin by such sensitized persons with the ordinary open methods. Methods of prevention of sensitization would be welcome. I am now using the Abbott syringe, so that I am not in contact with the drug or its vehicle.

I will go further than Dr. Rattner and say that while the reactions from penicillin are not so serious as from the sulfonamide drugs, I would not use penicillin in minor infections of the skin. I would reserve the use of penicillin for the more serious pyoderma, as I have advocated previously in the case of the sulfonamide drugs. It must be emphasized, in the meantime, that promiscuous use of the drug is unwise and hampers the use of a valuable agent when needed in the serious diseases due to organisms that are susceptible to penicillin.

DR. MARTIN F. ENGMAN JR., St. Louis: A group of us in St. Louis have conducted and published a clinical study of locally applied penicillin. A good deal of the work was done in the private office shared by Dr. Engman Sr. and me. We used penicillin ointment. Ten per cent of our subjects were irritated, usually rather severely. In patch tests, penicillin itself was found to be the offending agent.

There were no remarkable therapeutic results. Penicillin salve did not seem better as a therapeutic agent than older remedies such as microform sulfathiazole. It about equaled mercury or bismuth tribromphenate in impetigo. We do not use either penicillin salve or sulfathiazole in our office at present, since both are such strong sensitizers.

DR. HERBERT S. ALDEN, Atlanta, Ga.: Our experience with penicillin among combat forces in the United States Navy in the Philippines was similar to Dr. Lehmann's experience. For a period of some six weeks, we gave an average of 12,000,000 to 20,000,000 units of penicillin to men with combat injuries each day, and during that period I do not recall an instance in which we could consider penicillin a sensitizing agent.

After V-J Day we had some penicillin in excess. We began using it in a water-miscible base (the water-soluble base used by the United States Army or the base in any of the common shaving creams for impetigo and pyoderma). We would observe, as Dr. Rattner mentioned, waves of irritation after its use, and on investigation it seemed that the penicillin ointment which was prepared and left out on the counter (which was frequently true on a busy day) for more than forty-eight hours was the ointment that produced the irritation.

I have since felt (and it is just an impression) that the commercial penicillin ointments that had been on the druggist's counter for any length of time frequently produced irritation. Hence, in Atlanta, I have a druggist make up my penicillin ointment in a water-miscible base at regular intervals. I have noticed

The results of these experiments indicate that a superficial fungous infection may sensitize the skin so that the later administration of penicillin may provoke cutaneous reactions.

DR. FREDERICK R. SCHMIDT, Chicago: Just to complete the record, I would like to suggest the possibility of the use of penicillinase in these cases. I do not know how it could be used, but it is an agent which neutralizes penicillin promptly.

DR. H. J. TEMPLETON: I want to thank the various discussers for their generous contribution to my knowledge of this subject. I think I have learned more than I gave you. I have learned about the fatal reactions with which I had not had experience, such as generalized exfoliative dermatitis.

If you are doing any experimental work with patch tests, or if you are attempting passive transfer, you might remember that Kolodny and Denhoff showed that they did not get good patch tests, scratch tests or passive transfer unless they used, I think it was, 2,500 units per cubic centimeter. We were working with only 1,000 units per cubic centimeter.

I am aware of the dangers of penicillin, and I agree with Dr. Abramowitz and Dr. Engman that maybe it should not be used topically. I left a loophole in my paper, thinking that penicillin might be used with great care because of the excellent results which we have had in impetigo. For this disease we prescribe an aqueous solution of penicillin, 500 units per cubic centimeter administered with a DeVilbiss atomizer, and we tell the patient to spray the face three or four times a day. I have never seen anything work as rapidly in impetigo and with as little messiness.

## **THERAPY OF EARLY SYPHILIS WITH MASSIVE DOSES OF PENICILLIN**

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**W**HEN Ehrlich introduced arsphenamine (N. N. R.) in 1909 it was his sincere hope that syphilis could be cured with a single injection of the drug. It soon became apparent that one injection was woefully inadequate and, moreover, that three, six or even more injections failed to yield the desired result. With the introduction of bismuth as a powerful ally, the campaign against syphilis moved closer to its goal.

Two decades after Ehrlich's discovery, following the admirable work of the Clinical Cooperative Group,<sup>1</sup> it was generally recognized that the use of alternating courses of the arsenicals and bismuth preparations, given continuously over a period of approximately twelve to eighteen months, in a large percentage of cases, gave the result which Ehrlich had sought in vain.

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From the office of the President of the Chicago Board of Health and the Chicago Intensive Treatment Center, Venereal Disease Control Program, in cooperation with the United States Public Health Service.

1. Stokes, J. H.; Cole, H. N.; Moore, J. E.; O'Leary, P. A.; Wile, U. J.; Taliaferro, C.; Parran, T., and Usilton, L. J.: Cooperative Clinical Studies in the Treatment of Syphilis, *Ven. Dis. Inform.* 13:207 (June 20); 253 (July 20); 317 (Aug 20); 351 (Sept. 20); 371 (Oct. 20); 389 (Nov. 20) 1932.

In the early 1930's, a group of physicians<sup>2</sup> once again envisioned the possibility of eradicating syphilis in a short time by utilizing an intensified treatment—the "five day drip." A short time later, another group of investigators<sup>3</sup> sought to compress the treatment of early syphilis into one day, taking advantage of the therapeutic synergism of combining the arsenicals with physically induced fever.

At the onset of World War II, it was clearly recognized that long term routine antisyphilitic treatment could not cope with the threatened rise in venereal disease rates. From the standpoint of public health, it was deemed imperative to apply more widely the various intensive forms of treatment. Accordingly, centers were established throughout the country by the United States Public Health Service for the treatment of infectious syphilis in a relatively short time, arsenical and bismuth preparations with or without fever therapy being used.

In 1943, a clarion call was sounded by Mahoney, Arnold and Harris,<sup>4</sup> heralding an entirely new way of treating syphilis. Overnight the imagination of the medical world was fired by the dazzling prospect of a new and potent weapon in the battle against syphilis which dwarfed all previous drugs by virtue of its nontoxicity.

Numerous schemes of treatment came immediately to mind, and, indeed, many of them were projected into actuality. It was inevitable that Ehrlich's dream should flash forth again, embodying a new champion—penicillin.

Recent studies reported by Arnold<sup>5</sup> indicated that syphilitic rabbits treated with relatively massive doses of penicillin over periods of from twelve to twenty-four hours could be rendered nonsyphilitic. Thus, of 18 animals given 15,000 units at hourly intervals for twenty-four hours, 15 were successfully treated and in only 3 could any evidence of syphilis be found. The great differences in the course of the disease in rabbits as contrasted with that in human beings being recognized, an investigation was launched to determine the effect on human syphilis of massive doses of penicillin given over a short period.<sup>6</sup>

2. Hyman, H. T.; Chargin, L., and Leifer, W.: Massive Dose Arsenotherapy of Syphilis by Intravenous Drip Method: Five Year Observations, Am. J. M. Sc. **197**:480 (April) 1939.

3. Simpson, W. M.; Kendell, H. W., and Rose, D. L.: The Treatment of Syphilis with Artificial Fever Combined with Chemotherapy, Ven. Dis. Inform., 1942, supp. 16, p. 1.

4. Mahoney, J. F.; Arnold, R. C., and Harris, A.: Penicillin Treatment of Early Syphilis: A Preliminary Report, Ven. Dis. Inform. **24**:355 (Dec.) 1943.

5. Arnold, R. C.: Personal communication to the authors.

6. Schwemlein, G. X.; Barton, R. L.; Bauer, T. J.; Loewe, L.; Bundesen, H. N., and Craig, R. M.: Penicillin in Spinal Fluid After Intravenous Administration, J. A. M. A. **130**:340 (Feb. 9) 1946.

Of the patients 105 were Negro, of whom 68 were men and 37 women; 24 were white, of whom 17 were men and 7 women. Of the total number of cases, the conditions in 15 were in the seronegative primary stage and in 29 in the seropositive primary stage. Of the 85 patients in this series with secondary syphilis, 80 had early secondary syphilis and 5 exhibited late relapsing secondary syphilis.

Inasmuch as it is of interest to ascertain the promptness of relapse following treatment with a given scheme, the table reveals the relapse in the entire group at monthly intervals.

*Number and per Cent of Patients with Early Syphilis Treated with 10,000,000 Units of Penicillin from March 28 Through Aug. 2, 1945, Showing Number of Months After Treatment in Which Relapse Occurred*

Observation Period, Mo.			Failures				Clinically Negative				Status Unknown No. %	
	Total		Total		Probable Clinical Sero-logic	Probable Reinfection	Sero-positive		Sero-negative			
	No.	%	No.	%			No.	%	No.	%		
1	129	100.0	2	1.5	..	2	..	87	67.4	10	7.8	30 23.3
2	129	100.0	17	13.2	1	15	1	66	51.2	12	9.3	34 26.3
3	129	100.0	38	29.5	8	29	1	38	29.5	13	10.0	40 31.0
4	129	100.0	51	39.5	11	39	1	23	17.8	16	12.4	39 30.3
5	129	100.0	55	42.6	14	40	1	19	14.7	17	13.2	38 29.5
6	129	100.0	59	45.7	15	43	1	11	8.5	21	16.3	38 29.9
7	129	100.0	61	47.3	15	45	1	8	6.2	24	18.6	36 27.9

In 36 of the 129 patients included in "status unknown" observation was terminated for the following reasons: Two were inducted into the armed forces, 9 moved out of jurisdiction, 2 became pregnant, 4 were committed to jail and 19 we were unable to locate. Tests of the serum of these 36 patients gave negative results at the time of the last examination before they were lost to observation.

Not infrequently a patient failed to report to the hospital during one month and returned the following month. This accounts for the fluctuation in the column "status unknown" in the table.

#### COMMENT

It is apparent from the table that the rate of failure with this form of treatment under the conditions given in this experiment is so high as to render such treatment unsuitable for early syphilis. For 61 of the 129 patients discussed the treatment was a failure. Thirty-six of the 129 patients were not accounted for, having lapsed from observation. It is reasonable to assume that for some of these also the treatment was a failure.

It is interesting to note the relatively short time required for relapse to develop. Thus, in 51 of the 129 patients treated relapse occurred in four months or less.

# PENICILLIN IN THE TREATMENT OF EXPERIMENTAL SYPHILIS OF RABBITS

## III. The Therapeutic Activity of Penicillin by Oral Administration

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With the Technical Assistance of Anna M. Rule and Albert J. Paul

PHILADELPHIA

PENICILLIN by oral administration has not been reported on in the treatment of experimental or human syphilis. However, in view of the results observed in treatment of gonorrhea, pneumonia and other bacterial diseases of human beings by this route of administration, it was thought advisable to ascertain the possible therapeutic activity of penicillin in the treatment of experimental syphilis of rabbits by oral administration.

### METHODS AND MATERIALS

In our experiments all rabbits were inoculated intratesticularly with the Nichols-Hough strain of *Treponema pallidum*. Acute orchitis developed in all, with strongly positive results on dark field examinations about five to six weeks thereafter, when treatment was instituted. Dark field examinations were then made once a day for three days in succession and thereafter once a week over a total period of forty-nine days. At the expiration of this period the popliteal lymph nodes of surviving animals were inoculated into the testicles of fresh animals, which were kept under observation for a minimum of four months, when the results were evaluated.

The penicillin employed was a commercial amorphous sodium salt with an assay potency of 544 units per milligram, containing 88 per cent penicillin G, supplied by the Commercial Solvents Corporation (lot no. 45072102). For administration, solutions were freshly prepared in isotonic solution of sodium chloride containing 2,000 units per cubic centimeter.

Anhydrous sodium citrate was chosen as an antacid. Solutions were prepared in distilled water containing 0.1 Gm. per cubic centimeter. For administration the dose of penicillin per kilogram of weight was mixed with 2 cc. of the citrate solution (0.2 Gm.) and given by stomach tube at 9 a. m., 1 p. m., and 3 p. m. on each of ten days in succession, totaling thirty doses for each animal. As previously reported by Kolmer, Brown and Rule,<sup>1</sup> the free hydrochloride acid of the stomach

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From the Research Institute of Cutaneous Medicine.

1. Kolmer, J. A.; Brown, H., and Rule, A. M.: The Oral Administration of Potassium Bismuth Tartrate in the Treatment of Experimental Syphilis of Rabbits with a Note on the Gastric Chemistry of Rabbits, Am. J. Syph., Gonor. & Ven. Dis. 21:387 (May) 1937.

*Penicillin by Oral Administration in the Treatment of Acute Syphilitic Orchitis of Rabbits*

No.	Dose, Units per Kg.	No. of Doses	Total Dosage, Units per Kg.	Results of Dark Field Examination for T. Pallidum, Days *								Results of Transfer of Lymph Nodes
				1	2	3	7	14	21	28	35	
1.....	500	30	15,000	2	1	—	—	4	4	4	4	Positive
2.....	500	30	15,000	2	2	—	—	3	4	4	4	Positive
3.....	500	30	15,000	3	1	—	—	4	4	4	4	Positive
4.....	1,000	30	30,000	1	—	—	—	—	—	—	—	Positive
5.....	1,000	21	21,000	2	1	—	Died	—	—	—	—	Not done
6.....	1,000	30	30,000	2	—	—	—	—	—	—	—	Positive
7.....	5,000	30	150,000	1	—	—	—	—	—	—	—	Positive
8.....	5,000	30	150,000	2	—	—	—	—	—	—	—	Positive
9.....	5,000	30	150,000	2	—	—	—	—	—	—	—	Positive
10.....	10,000	30	300,000	1	—	—	—	—	—	—	—	Positive
11.....	10,000	30	300,000	1	—	—	—	—	—	—	—	Positive
12.....	10,000	30	300,000	1	—	—	—	—	—	—	—	Positive
13.....	15,000	30	450,000	1	—	—	—	—	—	—	—	Negative
14.....	15,000	30	450,000	1	—	—	—	—	—	—	—	Positive
15.....	15,000	30	450,000	1	—	—	—	—	—	—	—	Negative
16.....	20,000	30	600,000	1	—	—	—	—	—	—	—	Negative
17.....	20,000	30	600,000	1	—	—	—	—	—	—	—	Negative
18.....	20,000	42	840,000	1	—	—	Died	—	—	—	—	Not done

\* After treatment was instituted: 4 indicates large numbers of actively motile spirochetes per dark field; 3, 2 and 1 indicate smaller numbers of spirochetes per dark field respectively; — indicates negative results on dark field examination.

totaling 600,000 units, also yielded negative results on dark field examination and showed negative results on transfer of lymph nodes. In spite of these large doses, however, serum assays conducted one hour after the second and eighth doses showed no more than approximately 0.5 unit of penicillin per cubic centimeter.

#### COMMENT

In the circumstances, even relatively small doses of penicillin by oral administration, such as 500 units per kilogram, three times a day for a total of thirty doses (15,000 units) may yield temporarily negative results on dark field examinations. However, the minimal curative dose in the treatment of acute syphilitic orchitis of rabbits, on the basis of the results of transfer of lymph nodes, was between 15,000 and 20,000 units per kilogram three times a day for thirty doses, totaling between 450,000 and 600,000 units.

As previously reported,<sup>2</sup> the minimal curative dose of the compound in isotonic solution of sodium chloride by intramuscular injection was approximately 1,000 units per kilogram twice daily for eight days in succession, totaling 16,000 units. It is highly probable that the simultaneous administration of oxophenarsine hydrochloride or bismuth and potassium tartrate U.S.P. would have materially reduced the minimal curative dose of penicillin by oral administration through additive or synergistic effects. However, so far as penicillin alone by oral administration is concerned, a total minimal curative dose of approximately 500,000 units per kilogram in the treatment of acute syphilitic orchitis of rabbits would correspond to between 30,000,000 and 40,000,000 units in the treatment of early syphilis of human adults if the total dose required for the biologic cure of the latter was the same as that for acute syphilis of rabbits; this, however, is far from being true, since these animals require less per kilogram of weight. In the circumstances there appear to be no indications for oral penicillin therapy in the treatment of human syphilis unless, perhaps, it is subsequently learned that oral administration in conjunction with the administration of oxophenarsine hydrochloride or bismuth and potassium tartrate for additive or synergistic therapy is useful and acceptable under certain conditions.

#### SUMMARY

1. Relatively small doses of penicillin by oral administration, such as 500 units per kilogram three times daily for ten days in succession,

2. Kolmer, J. A., and Rule, A. M.: Penicillin in the Treatment of Experimental Syphilis of Rabbits: I. The Therapeutic Activity of Penicillin in Single and Multiple Doses in Isotonic Solution of Sodium Chloride and Peanut Oil-Beeswax by Intramuscular Injection, Arch. Dermat. & Syph. 55:741 (June) 1947.

totaling 15,000 units per kilogram, yield temporarily negative results on dark field examinations in the treatment of acute syphilitic orchitis of rabbits.

2. The minimal curative dose, however, according to the method of administration employed, varied between 15,000 and 20,000 units per kilogram three times daily for ten days in succession, totaling 450,000 to 600,000 units per kilogram.

3. Under the circumstances the oral administration of penicillin in the treatment of human syphilis appears to be contraindicated unless, possibly, it is combined with oxophenarsine hydrochloride or bismuth therapy for additive or synergistic effects in selected cases of the disease.

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Goodwin and Moore<sup>1b</sup> have already made such a compilation of the results of their own "Baltimore group" comprising 31 women with infectious syphilis during pregnancy (33 infants) and 26 women who were critically selected for infectious syphilis during pregnancy (27 infants) from the "Philadelphia group."

Since the total number in the two groups to date amounts to only 57 mothers with 60 infants, it appears of value to report the observations which were made at the Chicago Intensive Treatment Center on a comparable group ("Chicago group") of 36 women who were treated with penicillin for infectious syphilis during pregnancy and the effect of treatment with penicillin on their offspring.

The patients who were used in this project were selected with the following limitations. All mothers presented lesions of early infectious syphilis, and the presence of syphilis was confirmed by dark field examination in all cases, except 1, in which there were lesions indubitably characteristic of secondary syphilis but unsuitable for dark field examination. The infants were born not more than seven and one-half months after the diagnosis of syphilis and the beginning of treatment of the mother with penicillin. Antisyphilitic agents, other than penicillin were not administered to the mothers during the pregnancies, nor was the intensive course of treatment with penicillin repeated unless there was serologic or clinical evidence of relapse.

Out of a total of 265 syphilitic pregnant women, 42 fulfilled the aforementioned conditions and were due to have delivered by the date of this report (June 1, 1946). Of the 42 infants, 36 either were examined by us, or satisfactory reports of the status of these infants were secured. The other 6 infants either were moved from Chicago or could not be located. The present report is limited to the 36 infants and their mothers.

Inasmuch as it is pertinent to this study to compare the results of treatment of syphilitic pregnant women by one or another of the intensive forms of arsenotherapy with the results obtained by the use of penicillin alone, our tables were arranged after the pattern set by Goodwin and Moore.<sup>1b</sup> Thus, the results of treatment of the Chicago group are easily comparable with results for the Baltimore and Philadelphia groups (table 1).

Two summary tables (2 and 3) were prepared to compare the results of treatment with penicillin and with intensive arsenical therapy during pregnancy in preventing prenatal syphilis. In table 2 the results for the three groups that were treated with penicillin (Philadelphia, Baltimore and Chicago) were combined and compared with the results for the groups that received intensive arsenical therapy as compiled by Goodwin and Moore<sup>1b</sup> from the literature. In table 3 are presented the results of our examinations of 28 infants who were delivered of a

prolapse of the cord and asphyxia. This accident can hardly be attributed to the therapeutic procedure or to syphilitic infection. A second infant was reported stillborn (further information pending). The mother of this stillborn infant had secondary syphilis, as shown by dark field examination, seven weeks before delivery. She was treated with 2,400,000 units of penicillin over a period of fifteen days, starting seven weeks and ending five weeks before delivery. In this mother relapse of her lesions was demonstrated on dark field examination one month after delivery, requiring retreatment with 4,800,000 units of penicillin. Treatment in this case is regarded as a failure.

No signs or symptoms which could be attributed to congenital syphilis were detected in the 34 living infants by thorough physical examinations, serologic tests or roentgenologic studies of the long bones.

TABLE 2.—*Incidence of Prenatal Syphilis After Treatment of Early Infectious Syphilitic Mothers During Pregnancy*

Treatment	Incidence, Percentage	Total Cases
Intensive arsenotherapy	15	150 cases reported in the literature <sup>1b</sup>
Penicillin therapy.....	2.1	95 cases; Baltimore, Philadelphia and Chicago groups combined

TABLE 3.—*Infants Born of Mothers Who Were Treated for Infectious Syphilis During Pregnancy, Chicago Groups*

Treatments	Number of Infants Examined	Infants with Congenital Syphilis	Stillborn	Therapeutic Failures, Percentage
Intensive arsenotherapy .....	28	3	0	10.7
Penicillin therapy (2,400,000 units or more)	35	0	1*	2.8

\* Probably syphilitic.

Three of the 34 infants were reported as possibly premature. One infant was intentionally delivered six weeks prematurely by cesarian section (for bleeding placenta). The placenta was reported normal in appearance. The second infant was born one month prematurely and showed some signs of prematurity at 6 weeks of age. Further examinations at 2½ months and 3½ months of age revealed a perfectly normal infant with negative reactions to serologic tests for syphilis and normal long bones as determined by roentgenologic studies. The third infant was probably born one month too early. No signs of prematurity were detected on later examination.

In a fifteen year study of prematurity at the Lying-In Hospital in Philadelphia, Tyson<sup>3</sup> recently established that the average incidence of

3. Tyson, R. M.: A Fifteen Year Study of Prematurity, J. Pediat. 28:648 (June) 1946.

on dark field examination) four weeks after delivery, but the infant remained free of any evidences of syphilis. In the Baltimore group there were 3 women who, in the last trimester of pregnancy, had a serologic but no clinical relapse and were retreated with penicillin. The infants were normal at birth and remained free of congenital syphilis.

Two observations which were made in the Chicago group appear noteworthy. In both cases the mothers had mucocutaneous relapses (spirochetes were revealed on dark field examination) after treatment with penicillin and yet the infants remained free of syphilis.

TABLE 4.—*Duration of Pregnancy at Time Treatment Was Started*

Type of Therapy	Total Number of Patients	Number of Patients Pregnant		
		Less Than 16 Weeks	16-32 Weeks	More Than 32 Weeks
Penicillin.....	36	3	25	8*
Intensive arsenotherapy.....	28	5	21	2
Eagle.....	18	2	14†	2
Schoch.....	4	1	3	0
Fever, 8 hr. with 150 mg. bismuth compound and 60 mg. oxophenarsine hydrochloride....	6	2‡	4	0

\* One infant was stillborn; the mother had been treated with 2,400,000 units of penicillin from the seventh to the fifth week before delivery.

† Two infants were congenitally syphilitic. One mother was treated with 1,059 mg. oxophenarsine hydrochloride and 1,050 mg. bismuth compound the thirteenth to the fifth week before delivery. Mother's Kahn reaction was positive before and after delivery; she was retreated eight and one-half months after delivery. The other mother was treated with 1,380 mg. oxophenarsine hydrochloride and 675 mg. bismuth compound the tenth to the second week before delivery. Mother's Kahn reaction was negative three weeks before and two, three, three and one-half, four and five months after delivery. Serologic relapse and retreatment occurred one and one-half years after delivery.

‡ One infant was congenitally syphilitic. The mother was treated with fever-chemotherapy five months before delivery. The mother showed a negative (Kahn) reaction six, four and three weeks before delivery. There was mucocutaneous relapse seven weeks after delivery, and retreatment.

#### REPORT OF CASES

CASE 1.—A 14 year old pregnant Negro girl with secondary syphilis (spirochetes were present on dark field examination) was treated with 2,400,000 units of penicillin over fifteen days, twenty-one to nineteen weeks before delivery (May 17 to June 1, 1945). Her Kahn titer of 280 units on admission declined but remained at 40 units. On August 13 she presented herself, having relapsing secondary syphilis. The Kahn titer had risen to 200 units. In view of the advanced pregnancy 9,000,000 units of penicillin over a period of fifteen days was given in retreatment, six to four weeks before delivery (August 13 to August 28). On September 26, the patient delivered a full term, apparently normal, male infant, weighing 5 pounds  $\frac{1}{2}$  ounce (2,282 Gm.). The placenta was reported normal. The infant's serologic reactions were negative at the ages of 1 week,  $3\frac{1}{2}$  months and 8 months. A roentgenogram of the long bones revealed no evidence of syphilis. Physical examination revealed a lichen urticatus but no signs or symptoms of congenital syphilis. It is remarkable that the infant's reactions remained seronegative despite the mother's relapse, which is shown in the following tabulation:

1 day before delivery.....	20 Kahn units
1 week after delivery.....	Positive Kahn and negative Wassermann reactions
8 weeks after delivery.....	120 Kahn units

born, possibly because of syphilitic infection (2.8 per cent failures). In a strictly comparable group of 28 infants that were delivered of women with early infectious syphilis during pregnancy who were treated by various methods of intensive arsenotherapy, definite congenital syphilis (10.7 per cent failures) developed in 3 infants.

These observations on the Chicago group are in perfect agreement with the observations on the Philadelphia and Baltimore groups. The results for the three groups combined give an over-all incidence of 2.1 per cent of failure to prevent prenatal syphilis by the use of penicillin in the treatment of infectious syphilitic mothers during pregnancy as compared with 15 per cent of failure by intensive arsenotherapy which was reported in the literature by Goodwin and Moore.<sup>1b</sup>

#### CONCLUSIONS

1. Penicillin may be administered to the pregnant syphilitic woman with safety to both her and the fetus.
2. Of the various drugs which are used in the intensive forms of treatment and which are designed to prevent prenatal syphilis, penicillin is unexcelled.
3. Failure to eradicate the disease in the mother by treatment with penicillin is not inevitably attended by the birth of a child in whom congenital syphilis develops, even though the mother's relapse occurs a few weeks after delivery.

NOTE.—By July 15, 1947, when the proof was being read, a total of 81 infants delivered of women treated with penicillin for early infectious syphilis during pregnancy had been observed. Except for the 1 stillborn infant mentioned previously, the remaining 80 infants were free of infection to date. This would reduce our rate of failure with penicillin therapy from 2.8 to 1.24 per cent.

lesion filled in slowly and healed completely within the period of a month. Electrocardiographic tracings taken two weeks after the administration of the antitoxin revealed a diphasic T wave in lead IV, prominent Q waves in leads II and III and elevated S-T intervals in leads II and III. These changes reverted to normal two weeks later. Throat cultures became positive for *C. diphtheriae* on January 28 and did not become negative until March 1. The patient was discharged to duty on March 17 after one hundred days of hospitalization.

CASE 2.—T. M. B., a white woman aged 23, was hospitalized on Dec. 14, 1945 with the diagnosis of "contact dermatitis" of both hands. She was a nurse working in the ward of contagious diseases and there came in contact with cases of nasopharyngeal diphtheria. She gave a history of hay fever and an attack of contact dermatitis one year previously. On admission the palms revealed deep linear ulcerations in the region of the natural creases. The hands were erythematous, and the palmar surfaces of the fingers showed scaling. Therapy consisted of soaking the hands in solution of potassium permanganate and intramuscular



Fig. 1 (case 1).—Cutaneous diphtheria of the toe web (approximate duration, eight weeks; diphtheria antitoxin administered three weeks previously).

injections of penicillin. Despite this treatment the eruption became much worse. Decided edema of the hands and difficulty in flexing the fingers were noted. Numerous pustules developed on both hands. On December 27 cultures were reported positive for *C. diphtheriae*. On this date the patient received 100,000 units of diphtheria antitoxin after being desensitized. The improvement thereafter was dramatic. In forty-eight hours many of the pustules and the edema had disappeared. After exfoliation the underlying skin was pink, supple and healthy in appearance. The subsequent course was complicated by severe serum sickness and recurring secondary infections of the hands. Nose and throat cultures were negative on two occasions. The patient was evacuated to the United States on Feb. 15, 1946. The total time of hospitalization at this installation was sixty days.

CASE 3.—J. J. F., a white man aged 18, was admitted on Dec. 12, 1945 because of tinea cruris. Physical examination further revealed a small ulcerated area of the dorsum of the left foot near the base of the third and fourth toes. Local therapy consisted of soaking the affected parts in solution of potassium permanganate with good response of the crural lesion. However, on December 17 the lesion on the foot was noted to be "expanding." It presented a shallow ulcer

CASE 5.—R. B. B., a white man aged 29, was hospitalized elsewhere on Nov. 25, 1945 because of a lesion in the left inguinal region, which was thought to be secondary to scabies. In this area there was considerable erythema and excoriation, and in its center was a shallow ulcer approximately 2 cm. in diameter. The lesion became worse despite local therapy and intensive administration of penicillin. On December 11 a direct smear revealed "numerous bacilli resembling *C. diphtheriae*." The patient was given 70,000 units of diphtheria antitoxin. The following day a thick white membrane was removed from the base of the ulcer. On December 14 the base of the ulcer seemed to be much cleaner, and extension of the ulcer seemed arrested. On December 16 the patient was transferred to this installation. On the inner aspect of the upper part of the thigh was a shallow ulcer 5 cm. in diameter. The margins were sharp, and the base was covered by a purulent exudate. Cultures from the ulcer were positive for *C. diphtheriae* on December 16 and on Jan. 12, 1946. The reaction to the virulence test performed on the first culture was positive. The culture and the smear for *Hemophilus ducreyi* were negative. The Kahn reaction was negative. Further

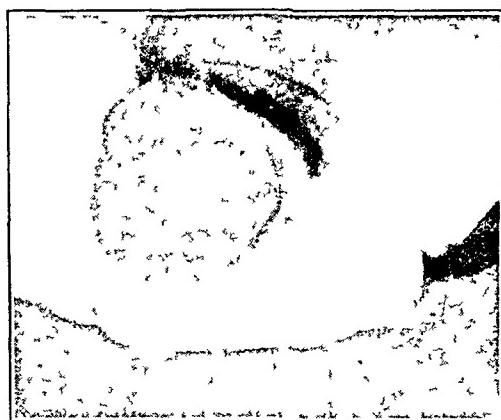


Fig. 3 (case 6).—Cutaneous diphtheria of the penis (approximate duration, seven weeks; diphtheria antitoxin administered one week previously).

therapy consisted of parenteral and local administration of penicillin. The lesion healed slowly. Repeated nose and throat cultures were negative for *C. diphtheriae*. Serial electrocardiographic tracings were normal. The patient was discharged to duty on February 11 after a total of seventy-eight days of hospitalization.

CASE 6.—S. J. H., a white man aged 26, was admitted to the Ninety-Seventh General Hospital on Dec. 17, 1945 because of a penile ulcer. The patient stated that after sexual intercourse on Nov. 24, 1945 he noted a laceration of the frenulum. Prior to admission two dark field examinations were negative for *Treponema pallidum*. A Kahn reaction was also negative. Physical examination revealed edema of the foreskin with paraphimosis. A large dirty ulcer extending almost completely around the shaft of the penis was present in the region of the coronal sulcus. Dark field examinations remained negative for *T. pallidum*. The Kahn reaction was negative on three occasions. Improvement was not noted after the administration of sulfadiazine by mouth and after local wet dressings. On Jan. 5, 1946 a positive culture for *C. diphtheriae* was reported, and the patient was given 100,000 units of diphtheria antitoxin. Penicillin therapy was started

January 26. Improvement of the lesions of both the hands and feet was rapid. Within seventy-two hours the purulent exudate disappeared, and the skin beneath the exfoliations was observed to be pink and healthy. Improvement thereafter was sustained. Nose and throat cultures were persistently negative for *C. diphtheriae*. Serial electrocardiographic tracings were normal. The patient was discharged to duty on March 3 after forty-eight days of hospitalization.

**CASE 8.**—W. V. G., a white man aged 25, was hospitalized elsewhere on Feb. 8, 1946 because of "sores on the penis." The physical examination revealed multiple punched-out ulcers on the penile shaft, scrotum and perineum and in the pubic region. Repeated dark field examinations were negative for *T. pallidum*. The Kahn reaction was less than 10 units. A culture from the penile lesions was positive for *C. diphtheriae* (reaction to the virulence test was positive), and the patient received 60,000 units of diphtheria antitoxin on February 12. Intensive penicillin therapy was also administered during the next seven days. A culture taken on February 16 was again reported positive, and two days later another 60,000 units of diphtheria antitoxin was administered. At this time great improvement of the lesions was noted. On February 24 a third culture was positive for *C. diphtheriae*, and an additional 60,000 units of diphtheria antitoxin was administered. The lesions healed satisfactorily, but persistently positive nose and throat cultures prompted the patient's transfer to the Ninety-Seventh General Hospital on March 6. On admission healed lesions of the genital area were present. They were erythematous, slightly scaling and not indurated, and each measured approximately 0.5 cm. in diameter. There were one lesion of the pubic area, four of the right hemiscrotum and four of the shaft and foreskin of the penis. The time required for healing of these lesions was approximately twenty-six days.

The following 2 patients were briefly observed while in transit. They were being returned to the United States because of complications following cutaneous diphtheria.

**CASE 9.**—J. K., a white man aged 23, was hospitalized elsewhere on March 6, 1946 with pustular lesions of the legs and lower part of the abdomen, which were thought to be due to secondarily infected scabies. Intramuscular administration of penicillin and local therapy resulted in improvement of all the lesions except an ulcer in the right inguinal region. This ulcer measured 1 by 2.5 cm. and was described as being covered by a thin grayish membrane. On March 19 a culture from the ulcer was reported positive for *C. diphtheriae*. After the administration of 80,000 units of diphtheria antitoxin the ulcer healed slowly, leaving a nonpigmented atrophic scar. On March 24 the patient began to complain of difficulty in swallowing and of inability to read. These symptoms disappeared within three days while, simultaneously, weakness of all extremities appeared. Definite decrease in the tendon reflexes was present. A slow recovery of strength took place over a period of sixty days, during which time the patient received physical therapy and thiamine hydrochloride intramuscularly. Serial electrocardiographic tracings were normal.

**CASE 10.**—A. L. L., a white man aged 19, was hospitalized elsewhere on March 15, 1946 because of "eczema" of both arms. By March 22 improvement had not been noted, and ulcers were observed on both forearms. Cultures taken from two separate ulcers were reported positive for *C. diphtheriae* on March 24, whereupon 100,000 units of diphtheria antitoxin was administered. The lesions

## CUTANEOUS DISEASES IN ARMY AIR FORCE PERSONNEL

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THE TYPE of dermatologic cases encountered in the Army differ somewhat from those seen in civilian practice. This is due to the fact that most of the chronic, serious or extensive cutaneous disorders are disqualifying for military service. In the Army, since it is composed mainly of healthly young men, one encounters mostly acute cutaneous diseases acquired after induction. This is especially true in the Army Air Forces, since the physical requirements for flying are so strict as to eliminate most cutaneous diseases.

The conditions of army life in training and combat make certain diseases of the skin commoner than in civilian life. Such is the case of scabies, dermatophytosis and dermatitis solaris. When one excludes the tropical diseases of the skin and the cutaneous diseases prevalent in tropical regions, which may be acquired by all types of personnel stationed in those areas, the incidence and the nature of different cutaneous disorders vary somewhat in each branch of the service.

The environment, the nature of duties, the instruments and the materials handled vary considerably in the ground forces, navy and air forces. In addition each individual assignment will bring personnel in contact with substances not used in another type of duty. All these factors will play a role in the production and persistence of cutaneous diseases. The substances or materials handled may lead to dermatitis venenata or may aggravate, by mechanical irritation or sensitivity, preexisting dermatoses. For these reasons the cutaneous diseases commonly encountered in the personnel of a destroyer, as shown by E. C. Kley,<sup>1</sup> will differ from those of a chemical warfare unit or a high altitude combat crew.

Some diseases are of greater importance in one branch of the service than in another, depending on the location of the disease and the type of duty of the patient. Such is the case in verruca plantaris and mild dermatophytosis, which may be incapacitating in a member of the infantry while they will be of minor importance in a navigator or a bombardier.

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This study was made while the author was serving in the Medical Corps, Army Air Forces, Army of the United States.

1. Kley, E. C.: Skin Diseases Aboard a Destroyer, U. S. Nav. M. Bull. 42: 407 (Feb.) 1944.

remains at altitude, individual susceptibility, environmental temperature, vascularity of the tissues and rate of blood flow. The more rapid the climb, the sooner the symptoms appear. At less than 30,000 feet (9,144 meters) they are rare, but at higher altitude they develop easily. The joints and the cerebrospinal, cardiovascular and the respiratory systems are affected. Tissues with a high content of fat are more prone to the formation of bubbles.

The skin plays an important role in aeroembolism. According to Armstrong,<sup>2</sup> cutaneous manifestations are secondary in frequency only to pains in the joints. There may be peripheral neuritis affecting the nerve endings. In such cases there is associated dermatitis with intense itching and burning of the skin of the area supplied by the nerve. This persists for several days. There may be macular eruptions or urticarial lesions covering the whole abdomen. Armstrong concluded that it would appear that the mechanical irritation of the gas bubbles on the posterior horn cells of the spinal cord may offer a clue to some of the neurodermal conditions whose causes are yet more or less obscure.

Other cutaneous manifestations of aeroembolism may be sensations of cold and heat, generalized tingling or formication. The last has been compared to "colonies of ants rushing madly over the surface of the body." It is likely that all these symptoms are due to nitrogen bubbles in the skin or fat of the subcutaneous tissue or of the nerve endings. Another factor which may affect the skin of a flyer is sudden changes of extreme temperature. In summer in the Southwest the average temperature inside a plane on the ground is 120 F. (49 C.). Shortly after a rapid ascent to an altitude of 30,000 feet the temperature averages —47 F. (—44 C.). To cope with these extreme changes closed cabins and specially made protective clothing are used.

The role of the skin in the regulation of the body temperature through perspiration and vasoconstriction is well known. Extreme cold temperatures may lead to frostbite. Its effect in aviation personnel has been reported.<sup>3</sup> Decreased tactile efficiency due to extreme cold has been observed. The effect of these sudden changes of temperature on normal and pathologic skin has not been determined. It seems reasonable to surmise that frequent repetition of these abnormal conditions will affect the cutaneous texture.

There are some chemical changes of the blood occurring at high altitude which may be important to the physiopathologic changes of the

2. Armstrong, H. G.: Principles and Practice of Aviation Medicine, Baltimore, Williams & Wilkins Company, 1939, p. 340.

3. Sheeley, W. F.: Frostbite: Eighth Air Force, Air Surgeon's Bull. 2:23 (Jan.) 1945.

regional hospital 6 to 8 patients were hospitalized monthly. At least half of these were transferred from satellite bases.

The ten commonest diseases of the skin encountered in air force personnel at the dermatologic clinic are shown in the table. Although most patients with cutaneous diseases were referred to the clinic by the station infirmary, where the patients reported on sick call, some patients with simple diseases were treated successfully there without the aid of dermatologic consultation. Therefore, the figures and percentages mentioned with each disease are intended only to give an idea of the incidence of the disease.

A study of the table will show that the most commonly observed disease was dermatitis venenata. In some instances this resulted from the application of strong ointments on acutely inflamed skin. In other cases it was due to overtreatment. In many instances the dermatitis resulted from contact with substances, materials and equipment handled

#### *The Ten Commonest Diseases of the Skin Encountered in Air Force Personnel*

	No. of Cases	Percentage
1. Dermatitis venenata.....	402	17.3
2. Pyodermas.....	352	15.1
3. Fungous infections and ids.....	206	8.4
4. Verrueae, all types.....	187	8.0
5. Urticaria, erythema toxicum.....	106	4.6
6. Dermatitis and eczemas.....	101	4.3
7. Neurodermatitis.....	96	4.1
8. Scabies.....	91	3.9
9. Acne vulgaris.....	88	3.8
10. Pompholyx-like eruptions.....	81	3.5

in the operations, repair or maintenance of aircraft. Pyodermas included deep, superficial and follicular pyogenic infections. Fungous infections, including dermatophytids, occupied only the third place, averaging 8 per cent of the total visits. Verruca vulgaris was the commonest type of wart seen. Verruca plantaris was decidedly rare. Dermatitis of unknown cause, eczema, scabies, acne and localized and generalized neurodermatitis were seen in approximately the same incidence. A peculiar superficial desquamation resembling dermatophytids or pompholyx was commonly seen. The dry and warm climate may have played a role in the production of this disease.

Among the rare diseases of the skin seen were scleroderma, tuberculid, dermatitis herpetiformis, erythema multiforme bullosum and lupus erythematosus. It is worthy of mention that no case of pediculosis corporis was seen and that pediculosis pubis was almost nonexistent.

#### CUTANEOUS DISEASES OF SPECIAL SIGNIFICANCE TO AIR FORCE PERSONNEL

*Dermatitis Venenata.*—Dermatitis venenata in personnel operating and repairing aircraft may be divided into two large groups: (a) derma-

Tetraethyl lead is an irritant to the skin and also produces systemic symptoms. Xylidin is highly toxic when absorbed through the skin.<sup>9</sup>

Dermatitis may be produced by large quantities of any of the primary irritants aforementioned. Small amounts of any of the solvents used may bring forth a dermatitis if a patient is hypersensitive to that particular substance.

*Dermatitis Venenata Produced by Equipment or Clothing Used by Flying Personnel:* Flying personnel are required to wear special clothing and equipment during operation. Heavy clothing is issued to protect them against cold temperatures. Different materials, varying from nylon to wool, come in contact with their skin, all of them being capable of irritation.

Another source of contact dermatitis is the rubber of earphones, goggles, throat microphones and oxygen masks. Cases of dermatitis venenata produced by those devices are not uncommon. In one of my cases dermatitis venenata developed every time the skin of the neck of a patient came in contact with the Bakelite disks of the throat microphone. This was proved by patch tests.

*Sycosis Vulgaris.*—Sycosis vulgaris is of much greater importance in the air force than in ground forces or in civilian practice. In the last two it is mainly of cosmetic interest. In flying personnel lesions of sycosis vulgaris may interfere with the proper fitting of devices essential to flying at high altitude, such as oxygen mask or throat microphones. Any disease of the skin which will hamper the proper fitting of these devices will handicap the efficiency of a flier. In cases of severe conditions it may prevent their use, thus incapacitating the patient in the performance of his duties or interrupting the training of qualified personnel.

The aggravating effect of dermatitis venenata due to rubber of oxygen masks and rubber and Bakelite of the throat microphones, together with the irritating action of the solutions used to clean these devices should be kept in mind. The mechanical action of friction associated with perspiration should also be taken into consideration as a possible cause of exacerbation. Occasionally, grounding a patient for one or two weeks has a beneficial effect. Special attention should be paid to the treatment of this disease in the early stages. Penicillin locally<sup>10</sup> and roentgen therapy usually gave satisfactory results.

*Acne Vulgaris.*—For the same reasons mentioned in the discussion of sycosis vulgaris, severe acne is a common cause of disability in flying personnel. The continuous friction and pressure exercised by oxygen

9. Parrish, H. C., and Byram, D. H.: Industrial Solvents in the AAF, Air Surgeon's Bull. 2:195 (July) 1945.

10. Canizares, O.: Penicillin in Dermatology: A Study of One Hundred and Seventy-Four Cases, Arch. Dermat. & Syph. 54:19 (July) 1946.

operation, repair or maintenance of aircraft. Sycosis vulgaris and acne are of importance in flying personnel. Dermatophytosis is seldom incapacitating.

4. There is surprising little information on the physiopathologic changes of the skin exposed repeatedly to flying at high altitude. There is great need for research in this field.

5. The importance of cutaneous disease in air force personnel varies according to its location and assignment of the patient. A thorough knowledge of his duties, the substances, materials and equipment he handles in his work is a great asset in the proper management of dermatologic patients.

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# AMINOPHYLLINE AS AN ANTIPRURITIC AGENT

## II. Intramuscular Injection

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A GENERAL report on the use of theophylline ethylenediamine (aminophylline) by injection as an antipruritic agent was presented in a previous paper.<sup>1</sup> It was demonstrated that this agent was most effective when administered intravenously. However, when the drug was given by this route, disconcerting immediate reactions, and even possible fatal reactions, limited its value in dermatology. The evanescence of the relief also indicated that further studies were necessary to make its use practical. The present report concerns the results obtained in 17 patients suffering with various itching dermatoses who were treated with intramuscular injections of aminophylline.

### MATERIAL

Seventeen patients were studied. The table briefly outlines the salient features in each instance. Thirteen patients were women, and 4 were men. All but 2 were white, and the others were Negro. The ages ranged from 31 to 71 years, roughly two thirds being between the ages of 41 and 60 years. In all instances the itching had resisted conventional antipruritic measures, including roentgen ray therapy in many. The diagnoses included many of the more resistant pruritic diseases. The dosage employed for all patients was 0.5 Gm. of aminophylline administered intragluteally in 2 cc. of fluid.

### RESULTS

In 7 patients the relief of itching was dramatic. The pruritus usually ceased within thirty to forty-five minutes and did not recur until twelve to thirty-six hours later. In 1 patient, a woman with eczema of the hands (case 7), one injection completely relieved all itching for a period of six days. This patient had failed to respond to treatment with the usual antipruritic agents over a period of one month.

Two patients, 1 with contact dermatitis due to vegetation (case 3) and 1 who had dermatitis due to dye in clothing (case 13), experi-

1. Epstein, E.: Theophylline Ethylenediamine as an Antipruritic Agent: Preliminary Report, Arch. Dermat. & Syph. 53:281 (March) 1946.

enced great relief, and in both instances injections quickly controlled recurrences.

However, the over-all results were not so successful in some of the other patients, who experienced temporary relief. Some needed daily injections to control the itching, and even then they failed to get well. This is exemplified by the response in the patient (case 16) who received nine daily injections for pruritus vulvae and pruritus ani and the patient (case 6) who was given seven injections for pruritus vulvae. While both were relieved by the injections, the itching promptly recurred as the effect of the treatment wore off.

*Outline of Cases Studied and Results Obtained in Seventeen Patients Treated with the Intramuscular Injection of Aminophylline*

Case	Age	Sex	Diagnosis	Number of Injections		Amount of Relief	Reactions
				1	3		
1	49	M	Generalized eczema .....	1	Little	Local	
2	52	M	Generalized dermatitis due to cement	3	None	Local	
3	36	F	Generalized dermatitis due to plants	17	Very decided.	Local; nausea	
4	50	F	Pruritus following scabies....	1	Patient failed to return		
5	46	F	Dermatitis of the arms and chest due to poison oak	2	Decided	Local	
6	46	F	Pruritus vulvae .....	7	Decided	Local	
7	41	F	Eczema of the hands.....	2	Very decided	Local	
8	31	F	Chronic urticaria .....	1	None	Local	
9	42	F	Contact dermatitis of the face	1	Some	Very severe local	
10	71	M	Generalized eczema due to plants	1	Little	Local	
11	56	F	Dermatitis venenata of the neck and chest	1	Moderate	Local; nausea	
12	34	F	Dermatitis of the hands due to plants	17	Decided	Local	
13	42	F	Dermatitis of the axillas due to dyes	6	Very decided	Local; menstruation	
14	62	F	Generalized pruritus .....	2	None	Local; general shock	
15	43	F	Generalized toxic dermatitis...	1	None	Local; nausea	
16	64	F	Pruritus ani and pruritus vulvae .....	9	Decided	Local	
17	56	M	Generalized dermatitis due to cement	2	Moderate	Local	

Six patients were sure that they experienced little or no benefit from the injections. In 3, only mild results were obtained. One patient (case 4) did not return for further observation.

#### REACTIONS

Aminophylline, as it is furnished for intramuscular injection, is in an alkaline solution. According to Kemp,<sup>2</sup> the addition of acid solutions of local anesthetics results in precipitation of their alkaloids. Therefore they cannot be added to the solution of aminophylline. Unfortunately, reactions to the injections are often painful. Variations of site and depth of the injection, as well as massage and exercise, did not help to alleviate pain, which occurred in all patients, but not on all

2. Kemp, R. S.: Personal communication to the author.

## COMEDOS LOCALIZED IN THE TEMPOROZYGOMATIC AREA

CHRISTOPHER DOUCAS, M.D.  
ATHENS, GREECE

TOWARD the end of 1944 and during 1945, 15 patients with an unusual eruption consisting of numerous comedos localized in temporozygomatic areas were seen by me in the outpatient department of the Evangelismos hospital. Such an eruption has not been described previously in our literature or in foreign literature.

Almost the same clinical picture was presented in all cases. This eruption was seen in 1 man; all the other patients were housewives between the ages of 25 and 60. The eruption consisted of symmetric patches of numerous small comedos localized in the temporal areas, extending from the ends of the eyebrows to the zygomatic bones and from the outer canthus of the eyes almost to the hair line. In 2 patients there was slight inflammation around the comedos. In 4 patients there was brownish pigmentation around the comedos, which resembled Riehl's melanosis. However, pigment was not seen in the corium on histologic examination. Comedos were not seen on the nose, cheeks, chin, chest or back except in 2 cases in which there were a few scattered comedos extending onto the cheeks.

A specific cause for such an eruption could not be determined, but many interdependent factors were suspected because of the abnormal living conditions that prevailed during the time this disease was observed. It was felt that the many dietary deficiencies and the substitutes prevalent during the war contributed to the appearance of the eruption in persons predisposed because of endocrinosympathetic disturbances, as occurs in Riehl's<sup>1</sup> melanosis.

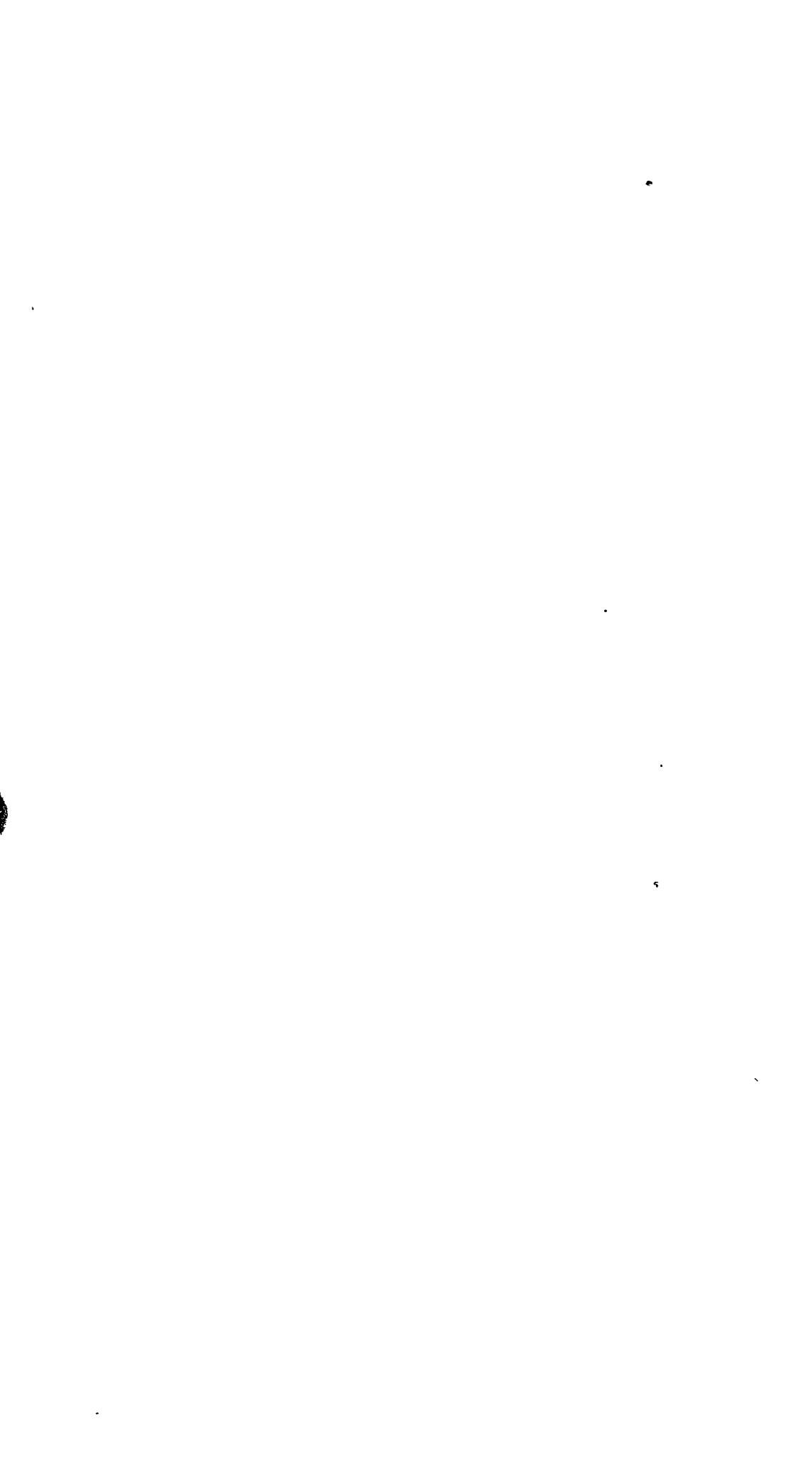
Nervous tension was considered to be important in the production of the disease. Berès<sup>2</sup> said that nervous shock can provoke hyperkeratosis of the sebaceous glands, and all these patients were neurotic. They cried without reason, trembled and were continuously in a state of excitement since the onset of the eruption at the time of the riots in

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From the Department of Dermatologic and Venereal Diseases of the Evangelismos hospital, Athens, Greece.

1. Riehl: Ueber eine eigenartige Melanose, Wien. klin. Wchnschr. 30:780 (June) 1917.

2. Berès, cited by Stannus.<sup>4</sup>



December 1944. Sex hormone balance was disturbed in most of the women during this time.

Substitute or inadequate foodstuffs may have been partially the cause of the eruption. Both wheat and fat substitutes were used during this period. Hyperkeratosis due to deficiency in vitamin A has been described by Frazier and Hu,<sup>3</sup> Stannus,<sup>4</sup> Sullivan and Evans,<sup>5</sup> Moult<sup>6</sup> and others said that deficiencies in vitamin B, C and E and in fatty acids provoked hyperkeratosis. These vitamins and fatty acids were lacking during the occupation of Greece.

The severe cold weather during December 1944 may have had some effect. Berès<sup>2</sup> stated that cold produces hyperkeratosis.

Since the eruption occurred primarily in women, the factor of the effect of the local use of cosmetics containing the substitute oil and ingredients obtainable during the war cannot be eliminated, although most of the women denied that they had used brilliantine, face cream or face powder. Garnier,<sup>7</sup> Gougerot<sup>8</sup> and Tzanck<sup>9</sup> reported such cases due to the use of brilliantine.

Histologic examination showed many keratinized cysts replacing the sebaceous glands. Some of the cysts were open on the surface, and others were closed beneath the epidermis. There was some atrophy of the hair follicles, and hairs were found below the cysts or even inside them. Hair was not found in other areas. There was flattening of the papillae and thinning of the prickle cell layer, and many of the cells were full of pigment. The granular layer was barely perceptible. The stratum corneum was normal. The blood vessels of the upper part of the corium were slightly dilated, and there was a little perivascular round cell infiltration. *Demodex folliculorum* was not found.

3. Frazier, C. N., and Hu, C.-K.: Cutaneous Lesions Associated with a Deficiency in Vitamin A in Man, *Arch. Int. Med.* **48**:507 (Sept.) 1931.

4. Stannus, H. S.: Vitamin A and the Skin, *Proc. Roy. Soc. Med.* **38**:337 (May) 1945.

5. Sullivan, M., and Evans, V.: Nutritional Dermatoses in the Rat: XI. Vitamin B Complex Deficiency, *Arch. Dermat. & Syph.* **51**:17 (Jan.) 1945.

6. Moult, F. H.: Histopathology of Rat Skin in Avitaminosis A, *Arch. Dermat. & Syph.* **47**:768 (June) 1943.

7. Garnier, G.: Boutons d'huile du visage par brillantine, *Bull. Soc. franç. de dermat. et syph.*, March 3, 1944, no. 3-4, p. 84.

8. Gougerot, H.; Carteaud, A., and Grupper: "Épidémie" de comédon par les brillantes, crèmes etc., de guerre, *Bull. Soc. franç. dermat. et syph.* p. 286.

9. Tzanck, A.; Sidi, E., and Dobkevitch, S.: Nombreux cas d'éruption acnéiforme provoqués par une brillantine de fabrication récente, *Bull. Soc. franç. de dermat. et syph.*, November-December 1945, no. 11-12, p. 293.

## TREATMENT

Quick response to treatment was obtained by the use of a solution of 2 per cent resorcinol in alcohol combined with simple extraction of the comedos. There was not any relapse of the disease.

## SUMMARY

Toward the end of 1944 and during 1945, 15 patients with comedos localized in the temporozygomatic areas and not accompanied by acne vulgaris or any evidence of inflammation were seen in the outpatient department of the Evangelismòs hospital. Fourteen of the patients were neurotic women between the ages of 20 and 60 years, who manifested varying degrees of ovarian hormone disturbance. Most of the patients did not use brilliantine, face cream or face powder.

30 Stournara Street.

began to lose his hair in patches. This loss of hair progressed for about five years, until he was totally devoid of hair, including eyelashes, eyebrows and body hair. This condition had persisted up to the time of his entering the hospital. Generalized itching had been present for a number of years, but a visible eruption had first become apparent about two and one-half years prior to admission. This had become more severe, with an accompanying inflammatory hypertrophy of the ears, nose, superciliary areas, chin and cheeks.

The patient stated he had lost the "pep" he used to have, but was not aware of any loss of weight.

Previous treatment had been carried out in a private clinic and had included various kinds of topical applications, low voltage roentgen ray therapy, ultraviolet irradiation, autohemotherapy, intravenous injections of strontium bromide, neo-arsphenamine and various other drugs. No relief had been obtained.

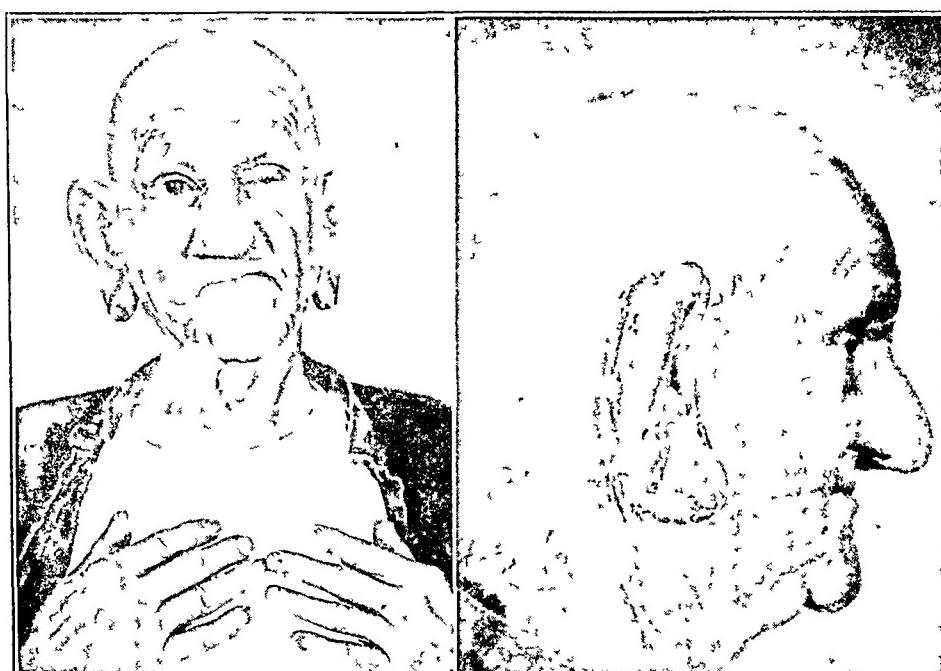


Fig 1.—Condition prior to treatment with testosterone, showing alopecia totalis and peculiar hypertrophy of nose, ears and face.

**Past History.**—The patient had typhoid forty years before entering the hospital. He had not had venereal infections, allergic manifestations or recent illness. He had lived in Mexico between 1902 and 1909 in a mining camp. His left eye was removed twelve years before admission after an injury. His ears had been draining a sticky material for six months. There had been no significant cardiorespiratory or gastrointestinal abnormalities. He had experienced nocturia two or three times with difficulty in starting urination, but with no burning. He had severe arthritis in the left shoulder for four months.

**Physical Examination.**—The patient was a well developed, well nourished man, who appeared to be older than 66 years. He was suffering obvious discomfort from a pruritic eruption. Hair was totally absent from the scalp, face and body. No significant lymph nodes were observed. The face presented a striking appearance, with some diffuse puffing and pronounced hypertrophy associated with

Hematologic studies made on Nov. 20, 1943 showed a hemoglobin level of 10.4 Gm. (65 per cent); red blood cells, 3,560,000; color index, 0.96, and white blood cells, 16,150. The platelets and neutrophils appeared normal, and the red blood cells were slightly anisocytotic. The differential count was as follows: neutrophils, 60 per cent; lymphocytes, 26 per cent; monocytes, 7 per cent, and eosinophils, 7 per cent. Comment by the hematologist: "The blood showed moderate monochromic anemia and slight eosinophilia. There was nothing in the peripheral blood of a leukemic nature."

Hematologic studies made on Jan. 17, 1944 showed a hemoglobin level of 12.8 Gm. (80 per cent); red blood cells, 4,040,000; white blood cells, 9,850, and reticulocytes, 0.5 per cent. The platelets were normal in number, and there was slight anisocytosis. The differential count showed: neutrophils, 62 per cent; lymphocytes, 26 per cent; monocytes, 3 per cent; eosinophils, 8 per cent, and basophils, 1 per cent. Comment by the hematologist: "The blood was probably normal, except for slight eosinophilia (Hodgkin's disease?)."

An examination of bone marrow, a specimen of which was obtained by sternal puncture, showed: polymorphonuclear cells, 50 per cent; metamyelocytes, 4 per cent; premyelocytes, 0; myelocytes, 1 per cent; myeloblasts, 2 per cent; eosinophils, 4 per cent; eosinophilic myeloblasts, 1 per cent; monocytes, 4 per cent; lymphocytes, 34 per cent, and monoblasts, 1 per cent. Comment by the hematologist: "The apparent increase in lymphocytes was probably due to laboratory technic."

Studies of the blood chemistry on Oct. 6, 1943 revealed a fasting glucose level of 80 mg. per hundred cubic centimeters; nonprotein nitrogen, 34 mg.; uric acid, 3.6 mg.; calcium, 10 mg.; albumin, 4.5 mg., and globulin, 3.5 mg.

A roentgenologic study of the chest on Dec. 20, 1943 revealed that "lung fields were overexpanded but otherwise clear. In the right lung, subapically, there was a Ghon lesion ("Ghon" complex—primary infiltration in lung with hilar lymphadenopathy) and calcification at the hilus. The aorta was redundant. No definite mediastinal adenopathy was identified at this examination."

A roentgenologic study of the lateral aspect of the skull on Oct. 22, 1943 showed that "the sella turcica was normal in size and shape. Calcification in the pineal body was at the anterior margin of the average in position."

**Histologic studies:** Biopsy specimens were taken from the ear and the forehead on three different occasions and were examined by Dr. Nelson Paul Anderson, dermatologic consultant in the department of pathology at the hospital.

The first specimens (figs. 3 and 4), taken on Oct. 4, 1943, were particularly notable for deep cystlike formations arising from greatly dilated follicles and surrounded by moderately heavy cellular infiltration composed mostly of lymphocytes, eosinophils and plasma cells. There were hypertrophy of the epidermis with elongated rete pegs and some dilatation of the capillaries of the upper layer of the cutis.

The second biopsy, on Nov. 5, 1943, was from the ear, and the structure suggested a peculiar type of basal cell epithelioma with cystic degeneration in the isolated groups of cells. This section had been misplaced and was not available for photomicrographing.

The third set of biopsies was made on Jan. 24, 1944 from the ear and the forehead, and the opinion was expressed that the observations were compatible with lymphoblastoma. Only one of the first and third sections was later available for photomicrographing, and it could not be determined whether the tissue was from the forehead or from the ear.



Fig. 4.—High power magnification of tissues seen in figure 3, showing the infiltrate composed of lymphocytes, plasma cells and eosinophils.



Fig. 6.—Little change in epidermis. Infiltrate seen in the upper layer of cutis.

On Nov. 11, 1943, the patient was referred to the rectal clinic for a search for foci of infection. Comment by the consultant: "There were several cutaneous tags, a small fistula and one infected crypt in the posterior part of the anus. Further search was deferred because of rectal pain. I believe that this patient should have surgical examination of the anus. He also should have the infected crypt and anal fistula operated on. Whether or not the pathologic changes listed constitute sufficient foci of infection to affect his skin is difficult to say."

On Nov. 2, 1943, the patient was referred to the ear, nose and throat clinic for examination for foci of infection, which revealed that the "tonsils were atrophic and had a few small crypts. There was a mucoid discharge, but the airways were otherwise clear. The small anterior cervical glands were palpable. Some crusting and scaling of the canals of the external ear were present. The tympanic membranes were fibrotic. No foci of infection in the ears, nose or throat were noted."

Treatment consisted of various types of topical applications, including wet compresses of solution of aluminum acetate, alibour water (water containing zinc and copper sulfates) and solution of boric acid, several types of shake lotions, three exposures of roentgen rays of 150 r each on the ears, autohemotherapy, various sedatives and a diet high in calories and in vitamins. No improvement resulted from these measures.

Administration of methyl testosterone by mouth in a dose of 10 mg. was begun on Nov. 11, 1943. The patient received a total of thirty-four doses each of 10 mg. except the doses which he received for a period of five days, which were of 20 mg. each. The medication was administered daily or on alternate days. When the patient was discharged, on Feb. 14, 1944, three months after treatment with testosterone was begun, his condition was definitely improved.

The patient was not seen again till approximately nineteen months later, when in response to a letter he reported to the clinic for observation. His appearance at this time was in striking contrast to his appearance at the time of his discharge from the hospital. His condition had continued to improve, so that he was able to return to work. He had experienced no relapse. The itching and inflammation had completely disappeared. The enlargement of the ears, nose and superciliary areas had subsided. There was still some enlargement of the ears, especially of the lobes, and also of the nose. The ears and the nose showed some evidence of hypertrophy of sebaceous glands with formation of comedos. There was a moderate growth of hair on the scalp, and the eyebrows, eyelashes and beard had regrown, although there was little hair on the body. The finger nails were normal. The general appearance of the patient was considerably less senile.

The patient stated that he had continued the use of testosterone by mouth for about one month after leaving the hospital, but that since then, or for a period of about a year and a half, he had taken no medication.

A urologic examination revealed a benign prostatic hypertrophy, which was consistent with the patient's age.

#### COMMENT

It is, of course, possible that the unusual combination of clinical manifestations encountered in this case were purely coincidental and bore no relationship to one another. This would appear unlikely, however, in view of the fact that all the symptoms began to disappear promptly on the administration of androgenic hormone. It would seem more probable that they were intimately related and constituted a peculiar symptom complex.

and the other 4 were considered to have been under treatment an insufficient length of time to have had satisfactory results. The treatment was given by subcutaneous injection with a dose of 10 mg. of testosterone propionate in the men and 1 mg. of estradiol dipropionate in the women at intervals of five to seven days. They did not consider the treatment as resulting in a cure because of a tendency to relapse, but felt that the benefit could be continued by maintenance doses.

Perhaps rhinophyma may be related to a deficiency of male hormone, or more properly, to the rather complicated changes associated with the male climacteric. So far as we know, no one has ever advanced this theory, and we are not acquainted with any observations bearing on this subject, although rosacea, which is a common precursor of rhinophyma, has in some cases in women been ascribed to hormonal changes associated with the menopause. However, rhinophyma occurs predominantly in men and severe rhinophyma occurs almost exclusively in men and usually in men past middle life. The process consists of hypertrophy of the sebaceous glands and follicles. It usually involves the nose and may involve the forehead, chin and cheeks. Involvement of the ears is probably rare.<sup>6</sup>

The clinical picture presented by our patient was obviously not of simple rhinophyma, but there were elements of rhinophyma in it. This was more apparent after the process had subsided. The hypertrophy of sebaceous glands of the nose and of the lobes of the ears is obvious in figure 2. It is conceivable that the peculiar appearance of our patient may have been due to a combination of senile pruritus and rhinophyma.

The lymphoblastoma-like infiltrate possibly represented a severe inflammatory reaction. The dystrophy of the nails may have been secondary to inflammatory changes of the skin with paronychia or to a primary hormonal effect, or may have been associated with the alopecia totalis.<sup>7</sup>

The subject of alopecia totalis and its relation to the entire picture is most interesting. The cause of alopecia areata and its extreme form, alopecia totalis, has been the subject of much debate, but no one has yet succeeded in establishing a definite causation. This disease may develop at any age and in either sex.

Waisman and Kepler<sup>7</sup> have studied the records of 138 patients with alopecia totalis who were examined at the Mayo Clinic and have drawn the following conclusions: 1. No gross clinical evidence of any

6. Senear, F. E., and Weichselbaum, P. K.: Rosacea and Rhinophyma (Nose and Ear Lobes), *Arch. Dermat. & Syph.* **52**:201 (Sept.) 1945.

7. Waisman, M., and Kepler, E.: Alopecia Areata: Appraisal of Endocrine Factors in Its Causation, *J. A. M. A.* **116**:2004-2006 (May 3) 1941.

consistent functional abnormality of the internal secretions could be observed. 2. The instances in which concomitant features of definite endocrine disease occurred were relatively few, and the associations appeared to be incidental rather than causal. 3. The unfavorable prognosis for the regrowth of hair in total alopecia was emphasized by the fact that only 4 of the 138 patients completely recovered. 4. Endocrine treatment up to the time of the report (1941) was ineffectual. 5. No other accompanying cutaneous disturbance in any of the cases was mentioned, except disturbances in growth and structure of the nails (pitting, longitudinal furrowing and thickening or thinning of the plates), which was frequently observed. There were also 9 cases of vitiligo and 3 cases of chloasma. 6. The age of onset ranged from 4 years to 69 years, with the greatest frequency in the decade between 20 and 30.

In the case of our patient it would be difficult to discount the influence of the testosterone in bringing about a regrowth of hair in view of the facts that the alopecia had been of fifteen years' duration and no other treatment, either local or systemic, had been used since the administration of testosterone was begun.

One might argue that the administration of testosterone should have an adverse effect on growth of hair in view of the common occurrence of baldness among men. Alopecia in men, however, is merely a pattern of distribution of hair determined by a combination of hereditary predisposition and the effect of the male hormone. In normal baldness in men, even in extreme cases, usually a fringe of hair about the sides and back of the scalp is left and the lashes, brows, beard and body hair are never affected. Hamilton<sup>8</sup> demonstrated conclusively the relationship between the male hormone and so-called premature alopecia in observations on a series of 54 sexually immature men who either were eunuchoid or had been castrated prepubertally or during adolescence. None of them presented this premature alopecia, in contrast with an incidence of about 43 per cent in normal adult men. After the administration of testosterone the typical male pattern of alopecia developed in the men whose family history showed a strong tendency to baldness.

There is no contradiction, therefore, in the apparent capacity of testosterone to stimulate growth of hair in the patient herein reported. It would be fallacious, however, to draw the conclusion that all cases of alopecia totalis are caused by deficiency in hormones or that a cure would result with hormone therapy. Normal pregnancies were recorded by Waisman and Kepler in several women with alopecia totalis, indicating no deficiency of sex hormones.

8. Hamilton, J. B.: Male Hormone Stimulation Is Prerequisite and an Incitant in Common Baldness, *Am. J. Anat.* **71**:451-480 (Nov.) 1942.

Rony and Zakon<sup>9</sup> reported the clinical and histologic effects of administration of androgen and estrogen in 2 apparently normal men. One man, who was 18 years old, presented an early but moderately extensive premature alopecia, and the other, who was 34, had subtotal alopecia areata. Methyl testosterone administered by mouth produced a definite stimulation and hypertrophy of sebaceous glands of the scalp in both men. A slight growth of lanugo hair with itching appeared in the bald areas of the scalp of the man with alopecia areata, who in addition to receiving 40 mg. of methyl testosterone by mouth daily for four months received 25 mg. of testosterone propionate twice a week by injection. The total effect of stimulation however was regarded as negligible. After a period of rest, however, and subsequent administration of 5 mg. of diethylstilbestrol daily for one month there was such a loss of scalp hair and other hair that the patient refused to take any more estrogen. The patient with premature alopecia received 5 mg. of diethylstilbestrol for three months without noticeable effects on the scalp hair, although there were definitely stimulating effects on the breasts. In both patients, biopsies revealed depressing effects with some atrophy of the sebaceous glands of the scalp.

Finally, a study of the photographs of our patient taken after he had recovered, or about nineteen months after he had left the hospital, gives the impression of a man five to ten years younger than he appears in the photographs taken during the height of his disability. The difference in appearance may, of course, be due in part to the growth of hair and the relief from intolerable itching.

#### SUMMARY

An unusual clinical picture is presented consisting of the case of a 66 year old man who had been totally bald for fifteen years and who later experienced a generalized pruritic eruption associated with inflammatory hypertrophy of the nose, ears, chin, cheeks and superciliary areas and decided dystrophy of the nails. Histologic examination of a specimen of tissue removed from the ear revealed a lymphoblastoma-like infiltrate in the cutis and decided dilatation of the follicles with cystlike formation. The entire clinical picture cleared up after four months of treatment with testosterone administered by mouth. When the patient was seen, nineteen months after his discharge from the hospital, the improvement had been maintained without further treatment, and there was a residual moderate hypertrophy of the sebaceous glands of the nose and ear lobes suggestive of rhinophyma of mild degree.

2007 Wilshire Boulevard.

9. Rony, H. R., and Zakon, S. J.: Effect of Endocrine Substances on the Adult Human Scalp, *Arch. Dermat. & Syph.* 52:323-327 (Nov.-Dec.) 1945.

## Obituaries

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### ARTHUR WHITFIELD, M.D.

1868-1947

By the death of Arthur Whitfield on Jan. 31, 1947, at the age of 79, dermatology has lost not only one of its outstanding figures but also a most attractive personality.

He studied medicine at King's College Hospital, London, and, after holding a number of junior appointments there, he spent three years, from 1893 to 1896, in Vienna and Berlin, attending the clinics of Kaposi and Neumann among others. On his return to England he was appointed dermatologist to the Royal Northern Hospital and later physician to the Skin Department at King's College Hospital, becoming Professor of Dermatology in King's College in 1906, which post he held until his retirement in 1927.

Among the leaders in dermatology in England at this time were Jonathan Hutchinson, Radcliffe-Crocker, Colcott Fox, Malcolm Morris, Pringle and Brooke, and as a member of the London Dermatological Society, then an exclusive society, he was able to study their methods and join them in their discussions. Of these men Colcott Fox influenced him most, and he for some time assisted him at Westminster Hospital. From Colcott Fox he learned to study cases with that care for detail which characterized his work during his whole career.

Entering the field of dermatology when knowledge of bacteriology and mycology of the skin was in its infancy, Whitfield threw himself with vigor into a study of these subjects. He published papers on the bacteriology of acne vulgaris and later, stimulated by the work of Almroth Wright, made a careful study of vaccine therapy in cutaneous diseases, opening a discussion on this subject at the International Congress of Medicine in 1913. He is best known, however, for his discovery of the causative role of fungi in tinea pedis. His observations, published in the *Lancet* in 1908, preceded by two years similar observations made by Sabouraud. This discovery was not a casual one, but the result of systematic microscopic examination of scales, which he always carried out. Later he introduced the ointment known by his name for the treatment of this disease, which, in spite of exhaustive investigations into new fungicides, still holds a valuable place in the treatment of fungous diseases.

The histology of the skin also intrigued him. He published papers on nevocarcinoma and osteitis deformans and, in conjunction with G. A. Harrison, a study of xanthomatosis. His work on erythema

Association, Inc., and always remembered with pleasure the meeting of the International Congress held in New York in 1907, which he attended.

Whitfield had a vivid and attractive personality. He seemed to possess perpetual youth. Even in his later years, when he was somewhat crippled by painful rheumatic spondylitis, this characteristic never left him. He had the curiosity of a boy and was never satisfied till he had found out all that there was to know about any problem which he attacked. At meetings he often threw fresh light on old problems and never hesitated to express his views in a vigorous manner. There can be no doubt that the influence which he exercised on his colleagues, especially his juniors, was far reaching and that by his death dermatology is poorer for the loss of an outstanding personality.

of this subcutaneous fat by infiltration of lymphocytes and organization of the thrombus appears plausible.

DR. MOLLEURUS COUPERUS: I do not believe that these lesions at any time were different from what they are today, except perhaps that they are a little lighter than they were four weeks ago. When I first saw the patient I thought that this was probably a transient eruption. The past history of the patient and the rather solid feeling of the margins of the lesions caused me to perform a biopsy. I believe that this patient does have sarcoidosis and more recent erythema induratum, an assumption which I think is supported by the microscopic sections from the two different lesions. The intense splenomegaly is not easily explained except by the assumption of sarcoidosis. Involvement of the eyes may also occur in this disease. The only question that one might have is whether the lesions on the legs are true Bazin disease or a deep form of sarcoid. The histologic picture does not seem to indicate the latter. From my perusal of the literature, it must be rare to see both sarcoidosis and erythema induratum simultaneously in a patient, but I believe that this is the case. The additional unusual feature is the erythema-annulare-like clinical appearance of the plaques, which are histologically erythema induratum.

**A Case for Diagnosis (Mycosis Fungoides?).** Presented by DR. SAMUEL AYRES JR.

**Sarcoid of Boeck.** Presented by DR. HARVEY STARR (by invitation) and DR. MOLLEURUS COUPERUS.

**A Case for Diagnosis (Lepra? Dermatitis Factitia?).** Presented by DR. A. FLETCHER HALL.

A white man aged 23, of American stock, who as a soldier had served in the North African and Italian campaigns, awoke one morning in March 1945 in Italy to find a red lesion on the right side of his forehead. The lesion did not subside, but gradually became scaly and has persisted practically unchanged for the past six months. Three months after the lesion was noticed a depigmented spot appeared on the front of the upper part of the right thigh. The new lesion, which was asymptomatic, gradually became enlarged, with loss of hair in the involved area. Later, central pinkness and scaling appeared. Since then numerous patches of a similar nature have appeared on the thighs and arms. The lesions progressed only to a certain point. There has been no itching.

The right side of the forehead is the site of an irregular, round, half-dollar-sized, mildly infiltrated, slightly pink and scaly plaque. The front and sides of both thighs show numerous irregularly scattered and depigmented round and oval patches in various stages of evolution. The youngest lesions are pea-sized depigmented patches, with irregular ill defined borders. The oldest lesions are larger and depigmented, with more regular well defined borders and loss of hair, while the oldest patches are similar but show in addition central erythema and scaling. The older lesions appear slightly infiltrated. A few lesions which appear bald show a few palpable tiny hair stubs near the center. The lesions are hyperesthetic to pinpoint stimulation.

The Wassermann and Kahn reactions of the blood were negative. No acid-fast bacilli were observed in curetted nasal material. No fungi were observed in microscopic examination of scales. Culture of scales on Sabouraud's medium yielded no growth. The blood count was normal.

Histologic examination of the lesion in the forehead showed that the stratum corneum was decreased in thickness and displaced from its normal attachment during fixation. No parakeratosis was seen. The stratum granulosum was thin

The patient suffered from gastric ulcers and arthritis but has not had a hernia, surgical treatment of the abdomen or varicocele.

On the scrotum, especially on the right side, are multiple, discrete, bluish red, elevated, matchhead-sized nodules. Capillaries are present on the scrotal skin.

The Wassermann and Kahn reactions of the blood were negative, and the urine was normal.

#### DISCUSSION

DR. L. F. X. WILHELM: I think that this case is a typical example of angiokeratoma of Fordyce.

DR. L. H. WINER (by invitation): In angiokeratoma there must be hyperkeratosis. Angiokeratoma occurs on the lower extremities after frostbite or trauma. Histologically, angiokeratoma is typical in that there is a large blood space covered by epidermis with a thick layer of stratum corneum on top. These lesions on the scrotum of the patient presented are more in the nature of angiomas. Keratoma is not part of it. It may be called an angioma of nevoid type, but not an angiokeratoma.

DR. SAMUEL TASKER (by invitation): Several months ago my colleagues and I had a patient with similar lesions. From histologic examination we concluded that "angiokeratoma" was a misnomer and that the lesions really were angiomas.

DR. SAUL ROBINSON: These cases are of interest since Fordyce first described a case of angiokeratoma about fifty years ago. A history of surgical treatment of the abdomen, hernia or varicocele with circulatory impairment is usual, and the patient is usually middle aged or senile. The angiokeratoma of Mibelli is observed in younger persons, with chilblain, or pernio. The lesions in angiokeratoma of Mibelli are keratotic, superimposed on angiomas and often seen on the dorsum of the fingers and toes.

#### Varicelliform Eruption of Kaposi. Presented by DR. A. FLETCHER HALL.

J. C., a white boy aged 15, had had eczema and asthma since he was 8 months of age. The eczema has been limited to the neck, cubital fossae and popliteal spaces, but more recently the hands and the lower part of the face have become involved. He had had herpes simplex in the past. Vaccination against smallpox was performed thirteen years ago.

He had been relatively free from cutaneous trouble all summer and until a week ago, about November 6, when the usual fall exacerbation began. On November 9 he suffered a chill and elevation of temperature in the evening. The next day his temperature rose to 103 F. and he noticed vesicles and pustules appearing in and around the preexisting eczematous patch in the left cubital fossa. Two days later the eruption became generalized and another chill and elevation of temperature occurred in the afternoon. On November 12 the eruption was at its height and another chill and elevation of temperature occurred. It was then that treatment with penicillin was begun in doses of 20,000 units intramuscularly every three hours. Since penicillin therapy was begun no new lesions have appeared, the fever has subsided and the patient feels much better.

The sides of the face and neck, the cubital fossae and the popliteal spaces show rather typical involvement with atopic dermatitis. There are a few similar plaques on the dorsa of the wrists and fingers. Superimposed on these patches and generally scattered over the entire surface of the body are numerous erythematous papules and ruptured vesicles or pustules, with dark crusts suggesting hemorrhage or even necrosis. The crusted lesions are more numerous on the face, neck, shoulders and arms. A few isolated intact varicelliform vesicles and pustules can

example, the person who acquires smallpox virus might be more severely ill than the one who acquires chickenpox virus or herpes virus.

DR. C. RUSSELL ANDERSON: I think that it has been well established that Kaposi's varicelliform eruption is due to the herpes virus. These patients have no immunity to the herpes virus, and that accounts for its appearance in children more often than in adults. I have observed 2 adults, both with atopic dermatitis, and both had Kaposi's varicelliform eruption. Neither of them had had herpes previously, but since their attack of the varicelliform eruption they have suffered attacks of herpes simplex. Immunity has not been established in them, and that is the reason for their widespread eruptions. I think that you will learn that persons with Kaposi's varicelliform eruption have never had herpes simplex. I think that in the past many of these cases have been classified as vesiculopustular erythema multiforme. Sutton's book has such an illustration by Sweitzer.

DR. A. F. HALL: I presented this case with the present diagnosis with misgiving, the reason being that there were a few points which did not conform to the diagnosis. However, several points have been brought out in the discussion which I want to clear up. The patient was decidedly ill prior to presentation, but he had been treated with penicillin. Perhaps this case should have been presented as one of dermatropic virus infection superimposed on an atopic dermatitis. He has had repeated attacks of aphthous stomatitis, which I believe is due to the herpes simplex virus. If this disease were to become disseminated, I believe that the eruption would have developed before now. I think that there are other viruses which may cause a similar eruption. If his mother, who is a registered nurse, were not so certain that the patient had had varicella at the age of 3 years, I would be inclined to suspect that disease superimposed on atopic dermatitis. At present this eruption certainly is more disseminated than that in the cases of Kaposi's varicelliform eruption described by Dr. Goeckerman and others. Dr. Goeckerman mentioned seeing such cases in persons in certain localities. In the past year in Santa Monica, Calif., I have seen 2 cases, both in infants under 2 years of age, and both have been cases of typical appearance and history, almost limited to the areas of preexisting atopic dermatitis.

NOTE.—On the fourteenth day after the onset of this patient's eruption, his brother experienced typical severe varicella. His mother still maintains that both the patient and his brother had previously had varicella in childhood.

#### A Case for Diagnosis (Lymphedema?). Presented by DR. ANKER JENSEN.

A. L., a white man aged 50, was presented on March 9, 1943 (*Arch. Dermat. & Syph.* 48:475 [Oct] 1943). Since then the lesion has become enlarged. No treatment has been given. The mass extends slightly into both nostrils, including most of the upper lip to a width of about 5 cm. The consistency is doughy.

#### DISCUSSION

DR. M. E. OBERMAYER: I think that the tumor mass has become enlarged since this patient was presented for the first time and looks today more like typical elephantiasis than it did then. Moreover, the possibility of an angiomatous tumor has now been ruled out by biopsy.

DR. J. WALTER WILSON (by invitation): This localized lymphadenopathy around the face and nose, I was interested to learn, had another name, "Erysipeloid of Fox." It is, as I believe Dr. Obermayer commented two years ago, a bacterial plugging of lymph channels from areas in the face, around the nose mostly. In most of these cases the disease recurs several times before lasting changes are produced. In this patient apparently the feature of recurrence is not present.

DR. L. H. WINER (by invitation): I agree with the diagnosis because the histologic picture is definitely that of balanitis xerotica obliterans. There is atrophy of the epidermis and homogenization of the upper layer of the cutis, with a band of lymphatic infiltration beneath the homogenized zone.

MAJOR R. L. SANDERS (by invitation): I felt that the clinical course was characteristic. It is a chronic slow process. The histologic picture fitted in fairly well with the picture of the case reported by Laymon. I was interested to learn the relationship between this disease and lichen sclerosus et atrophicus.

**A Case for Diagnosis: Lichen Ruber Moniliformis (?), Dermatitis Actinica from Roentgen Ray Therapy of Legs. Presented by DR. MAXIMILIAN E. OBERMAYER.**

E. P., a white woman aged 45, of American stock, at the age of 12 had mosquito "bites" all over the body while on a camping trip in the mountains of Pennsylvania. The "bites" subsided with the exception of those on the legs, which she scratched, thus preventing their healing and causing the formation of "open sores," which were thought to be from "dye poisoning" from the stockings. The "sores" persisted and were left untreated until the age of 16, when a physician in Philadelphia administered an injection of arsphenamine ("606") and continued what was evidently antisyphilitic therapy for one and one-half years. The "sores" healed rapidly, but a pruritic eruption remained and has persisted until the present time. A course of roentgen ray therapy was given in 1933. In the years which followed the skin over the irradiated area became thinned, and from 1936 on she has been suffering off and on from multiple ulcerations.

The patient was said to have been presented before a dermatologic society at Syracuse, N. Y., about fifteen years ago.

The skin from just above the knees down to the ankles is covered with flat, slightly erythematous or waxy, densely set papules of moderately firm consistency, from 2 to 4 mm. in diameter, which form almost confluent plaques in some places but have a beadlike arrangement in others. In addition, the skin above the shins is atrophic and covered with fine telangiectases, and in the center of the right shin is a shallow ulcer of 1 cm. in diameter.

The complement fixation reaction of the blood was positive. Microscopic examination of one of the "waxy" papules outside the irradiated area revealed a wide band of hyperkeratosis, thickening of the granular layer to three layers and mild acanthosis in the epidermis. The predominant change in the dermis was vascular dilatation, which involved all the vessels and lymph spaces. There was slight swelling of the walls of the vessels and a scarce perivascular lymphocytic infiltrate. A section stained with methylrosaniline chloride did not reveal amyloid.

#### DISCUSSION

DR. W. T. GOECKERMAN: To me this is a rare and distinctive, if not classic, picture. I have seen probably half a dozen cases of this type over the years, and clinically they closely resemble each other in their appearance and behavior. I believe that they do not belong in the same category with lichen planus but are more closely related to neurodermatitis. For want of a better term I have called them "lichen ocreaformis." Possibly the coiners of this term would take issue with me. However, I maintain that these cases are of a distinctive group. I recall 2 patients that were studied intensively and whose confidence I gained. They were constantly plagued by recollection of sexual experiences of a profoundly abnormal character. I cannot help feeling that any therapy of value in these cases must be based on carefully planned psychotherapy.

## Book Reviews

**Studies on Acarus Scabiei and Scabies.** By Bjørn Heilesen. *Acta dermatovenereologica*, volume XXVI, supplement XIV. Pp. 370, with 63 illustrations. Copenhagen, Denmark: Rosenkilde and Bagger, 1946.

The investigations dealing with the scabies mite and the eruption of scabies started in 1942 at the dermatovenerological outpatient clinic of the Kommunehospital and at the University Institute of Histology and Embryology in Copenhagen, Denmark. The studies were continued in 1943 at the dermatovenerological department of St. Göran's Hospital (chief: Dr. Bo Tarras-Wahlberg), at the dermatovenerological clinic of Kungliga Karolinska Institutet (chief: Prof. Sven Hellerström), and at the entomologic department of the Natural History Museum in Stockholm. In 1945 the studies were brought to an end at the dermatovenerological Clinic of the University of Copenhagen, at the Rigshospital (chief: Prof. H. Haxthausen).

This book consists of two parts. The first part deals with a historical survey of the morphology, biology and internal anatomy of the acarus and with sensitization of the human skin to the mite. The second part deals with the author's own investigations in regard to the anatomy of egg, larva, nymph and adult mite, the internal anatomy of the mite, the developmental cycle of the acarus and the sensitivity of the skin in patients with scabies and in control persons.

There are 63 illustrations dealing with the anatomy of the mite, including diagrams and photomicrographs of the mite in the tissue and photographs of reconstruction of the burrow.

This book was written as a thesis for a doctorate and contains an enormous amount of detailed scientific work.

**X-rays and Radium in the Treatment of Diseases of the Skin.** By George M. MacKee, M.D., and Anthony C. Cipollaro, M.D. Contributor, Hamilton Montgomery, M.D. Fourth edition. Price, \$10. Pp. 668, with 321 engravings and 4 colored plates. Philadelphia: Lea & Febiger, 1946.

The fourth edition of this textbook maintains the high standard of excellence established by its predecessors. It is a most useful product of the many years of research and experience of its two authors in the treatment of diseases of the skin with roentgen ray and radium.

In the third edition a number of collaborators contributed to and helped revise the individual chapters. This is not so in the present edition, but much of the material which was added by these collaborators has been retained. The book has been made more compact and, in the opinion of the reviewer, more readable by the elimination of some material, such as the chapter on roentgen ray spectroscopy. This subject, according to the authors, defies simplification and has a limited field of usefulness to the average dermatologist.

The arrangement of material is essentially the same as in previous editions, progressing from the historical aspects through sections devoted to physics, technic, pathology and the methods of treating individual diseases.

The chapter on the pathologic histology of radiodermatitis is contributed by Dr. Hamilton Montgomery and is enhanced by the addition of two colored plates illustrating chronic radiodermatitis and radio epidermitis. New material includes discussion of epithelitis and epidermitis, terms applied to the cutaneous and deeper reactions associated with protracted fractional treatment of either cutaneous or internal malignant lesions, according to the principles outlined by Contard.

The illustrations are excellent throughout the book. Many useful charts accompany the text, and a bibliography follows each chapter.

The book cannot be too highly recommended for use by all who treat diseases of the skin with roentgen ray and radium.

cytoplasm. These droplets fuse, replace the cell cytoplasm and combine with similar droplets from surrounding degenerating fibrous tissue cells.

King,<sup>1</sup> of Australia, has done some work staining the Golgi apparatus of connective tissue cells, which he felt proved that the mucoid material is produced by the increased secretory activity of fibrocytes returning to embryonal forms because of the stimulation of mild trauma. However, it is my belief as well as that of other observers<sup>2</sup> in this country that the mucoid material is a product of degeneration.

Some observers<sup>3</sup> postulate the mucoid degeneration of a fibroma of the skin or periarticular subcutaneous tissue. A careful review of the history in my cases gave no indication of previously existing solid tumors.

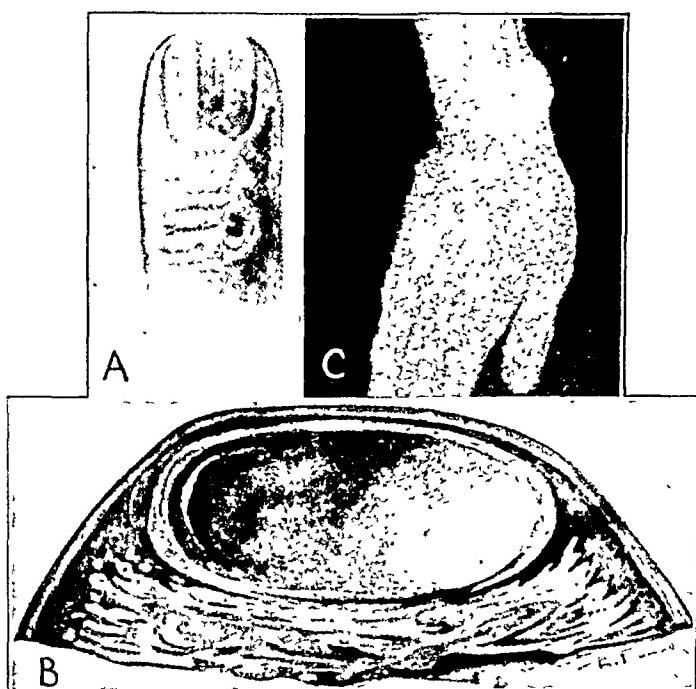


Fig. 1.—A, myxomatous degeneration cyst of the finger. B, cross section of myxomatous degeneration cyst of the finger. C, typical myxomatous degeneration cyst of subcutaneous tissue of the wrist.

Ideas on pathogenesis<sup>4</sup> fall into these main groups: (1) herniation of tendon sheaths, (2) tears of tendon sheaths with lakes of syno-

1. King, E. S. J.: The Formation of Ganglia and Cysts of the Menisci of the Knee, *Surg., Gynec. & Obst.* **7**:150, 1940.

2. DeOrsay, R. H., and others: Pathology and Treatment of Ganglion, *Am. J. Surg.* **36**:313, 1937.

3. (a) DeOrsay.<sup>2</sup> (b) Savatard, L.: Periarticular Fibroma of the Skin ("Synovial" Lesions of the Skin), *Arch. Dermat. & Syph.* **9**:441 (April) 1924.

4. King.<sup>1</sup> DeOrsay.<sup>2</sup> Savatard.<sup>3b</sup> Gross, R. E.: Recurring Myxomatous Cutaneous Cysts of Fingers and Toes, *Surg., Gynec. & Obst.* **65**:289, 1937.

tendon sheath), also is not the best scientific term to apply to the deeper lesions. It is suggested that the name which I have applied to these lesions, myxomatous degeneration cysts, be adopted since it describes the pathologic changes and also gives a more exact idea of the nature of the process.

A review of the literature and the study of my cases have led to the conclusion that myxomatous degeneration lesions, both the former synovial cysts of the fingers and the ganglions of the hands, wrists,

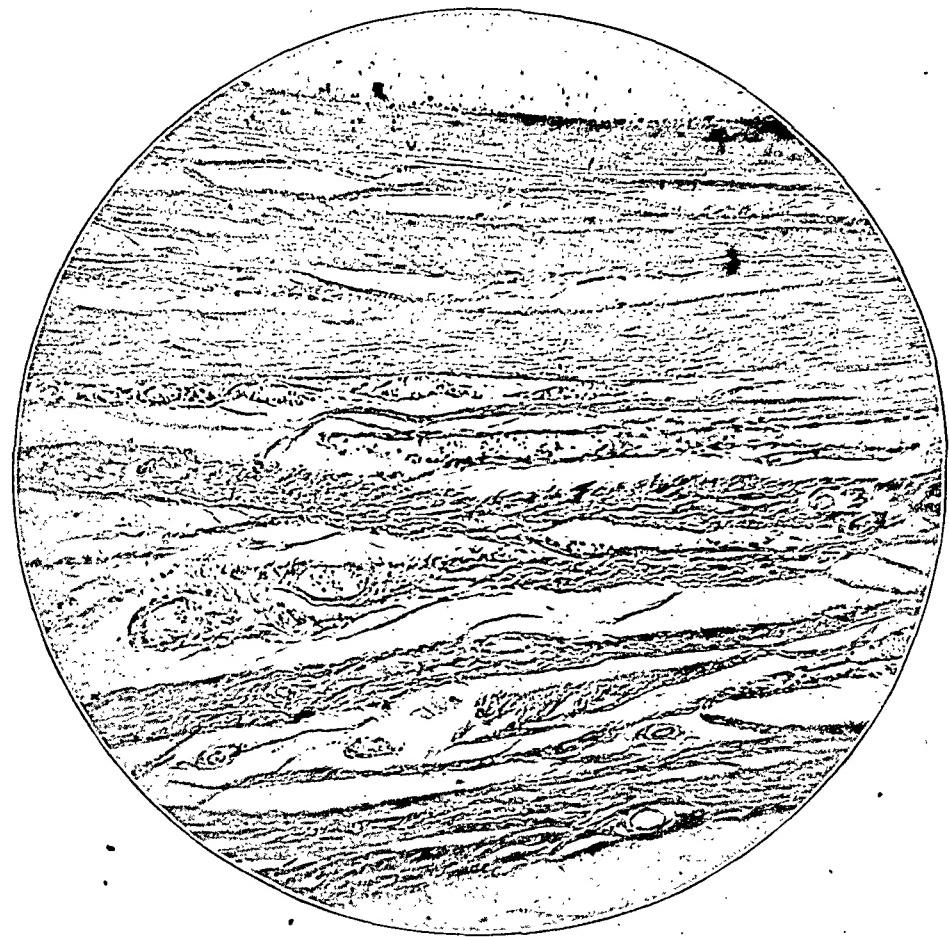


Fig. 3.—High power magnification of a cyst from the wrist, showing absence of lining membrane. The lining is made up of flat fibrocytes.

ankles and feet, are degeneration lesions of fibrocytes in which the cells produce a myxomatous material and in which, by fusion of many small cysts, the clinical lesions, as we know them, are formed.

The location and type of lesions lead to the conclusion that probably friction, pressure and repeated minor trauma are the main factors in the formation of these cysts.

unsatisfactory in my hands. However, Reeves<sup>10</sup> had recently reported 87 per cent cures with a technic of administering 200 r through 0.5 mm. of copper and with one dose each month. Two, three or four doses have usually been necessary. Lyle<sup>11</sup> has reported 81 per cent cures in 8 cases in which treatment was with a similar technic.

When it was decided that a reaction had to be produced to obtain satisfactory results the dosage was increased and various technics applied.

Ten patients were treated with a peak of 150 kilovolts through 3 mm. of aluminum and two doses of 400 r each, three weeks apart. With this treatment local reaction was limited to slight erythema, and residual atrophy was not seen. Five of the 10 patients had a permanent result. In 5 there was a recurrence, usually within two months, or failure of the cyst to disappear.

Five patients were treated with a peak of 200 kilovolts through 3 mm. of copper and two doses of 400 r each, three weeks apart. Results were no better with the increase in kilovoltage and filtration, so that this method was discontinued.

Ten patients were then treated with a peak of 150 kilovolts through 3 mm. of aluminum, and three doses of 400 r each, one week apart. This group gave a result of 70 per cent cures after three months.

Ten more patients were then treated with roentgen rays, filtered through 3 mm. of aluminum in two doses of 500 r each in one week. In these patients moderate erythema developed, usually followed by some superficial desquamation. The cyst disappeared in all these cases, so that in the balance of the cases treatment was with this technic. In later follow-up in these cases an area of superficial atrophy was seen, with depigmentation and patchy hyperpigmentation. The skin was soft; there was no tenderness, and permanent results were obtained in all cases on the fingers.

In deeper lesions of the wrist, ankle and dorsal surface of the hand and foot there were 80 per cent permanent results.

Disadvantages of the treatment are the resulting area of atrophy, with some depigmentation and patchy hyperpigmentation. In certain cases the production of a small atrophic area is not a too serious sequela.

One of the typical cases is that of a physician's wife, who was a pianist. A nodule developed on the dorsal surface of the left wrist, which was painful if she practiced on the piano for any length of time.

10. Reeves, R. J.: Radiation Treatment of Ganglia of the Wrist, *South. M. J.* **37**:584, 1944.

11. Lyle, F. M.: Radiation Treatment of Ganglia of the Wrist and Hand, *J. Bone & Joint Surg.* **23**:162, 1941.

The lesions had been surgically excised on several occasions, with prompt recurrence. Roentgen ray therapy produced complete relief of pain in a week, with disappearance of the nodule in three weeks.

Occasionally the nodule has failed to disappear for four weeks. Retreatment in a few cases over the same area has increased the percentage of cures. In a few cases nodules have recurred in adjacent areas. These have usually responded to treatment as well as the initial lesion.

Some believe that microscopic study of all nodular lesions should be undertaken to exclude malignant lesions. However, careful review of the literature has shown no cases of malignant degeneration of these myxomatous cystic lesions.

#### CONCLUSION

Ganglions, synovial cysts and like lesions are a myxomatous degeneration of fibrous tissue cells of the dermis, aponeuroses or other fibrous structures. Histologically they are identical and are produced as the result of minor trauma and friction.

Treatment with roentgen rays with a peak of 150 kilovolts through 3 mm. of aluminum and two doses of 500 r each in one week has produced the most satisfactory results of any known method of treatment. Disadvantages of this treatment are commented on, and it is my belief that in most cases, particularly when symptoms are produced by the lesions, the slight residual atrophic patch is not too great a contraindication to this method.

If some should believe that the residua are a contraindication to the use of this as a primary method, it would still be of importance in the treatment of lesions in the many cases in which there is recurrence after simple excision.

434 Metropolitan Building.

#### ABSTRACT OF DISCUSSION

DR. HARTHER L. KEIM, Detroit: I should like to congratulate Dr. Woodburne on his convincing presentation, not only on the manner in which he handled this abundant material and the conclusions that he drew but, in particular, his attempt to simplify once again and correlate terminology. Such efforts always appeal to me. While the problem of terminology is here not nearly so urgent as in pachyonychia congenita, as was outlined for us yesterday by Dr. Montgomery, it would seem that if synovial cysts of the fingers, ganglions and some of the epidermal cysts have a common pathologic basis and are myxomatous degeneration cysts, then such a term should be used to cover this particular group of diseases.

Dr. Woodburne has convinced me that these lesions, the so-called myxomatous degeneration cysts, have nothing to do with the synovial system. We will find in both dermatologic and surgical literature a diversity of opinion expressed as to their relationship with the synovial system. Here in this audience are a number of persons who have expressed different opinions on each side of this question.

I think that the fact that these cysts have no endothelial or epithelial lining and that the content is definitely mucoid certainly leaves this group of diseases without any association with the synovial tendon.

With reference to treatment, it has been my experience that up to the present time surgeons are usually best qualified to attempt complete removal. Dr. Woodburne has, however, called attention again to the fact that surgical approach is not always satisfactory. Consequently, I feel that his recommendations with reference to roentgen ray therapy should be borne in mind, especially for patients with small lesions, in whom this rather sizable dose would probably not result in radiation dermatitis.

DR. H. J. TEMPLETON, Oakland, Calif.: The lesions on the dorsum of the knuckle are old enemies of all of us. We have all treated many of them, I am sure. My own therapeutic results have been poor. I have treated these lesions by simple excision; I have treated them by electrocoagulation followed by curettage and reelectrocoagulation and by destruction with actual cautery, and they have recurred rather uniformly.

I am glad to hear Dr. Woodburne tell about his results from roentgen rays, because possibly I will try it again, but I have given many of these lesions 1,500 roentgens, with a peak of 90 kilovolts, unfiltered, or treated them for three hours with a half-strength 10 mg. radium plaque, with 1 mm. of brass filtration, which is effective in plantar warts, and nothing has happened except an erythematous reaction of the lesion and a persistence or recurrence of the cyst.

My practice now is to tell patients that these lesions are harmless and that they do not have to be treated unless they are sufficiently annoying. If they think that treatment is necessary, I refer them to an orthopedic specialist who does a rather interesting operation. He excises the lesion which is on the dorsum of the knuckle, makes a U-shaped flap on the lateral border of the finger and swings that up, covering the denuded area. His results in the few patients I have referred to him have been good in comparison with mine, which have been poor.

DR. RICHARD L. SUTTON JR., Kansas City, Mo.: Dr. Woodburne has made the valuable and practical point that suitable roentgen ray therapy is extremely effective and should be the first choice of therapeutic effort in such cases. I believe that his success depends partly on irradiating a wide enough area, rather than screening down too close to the exact edge of the lesion, for peripheral fibrotic tissue can undergo myxomatous degeneration and so lead to recurrence. Such, perhaps, is the explanation of recurrence after operation.

In electing surgical treatment, one does not hesitate to produce scarring and permanent alteration when these are inescapable. Radiologic therapy may deliberately and unhesitatingly scar, too, given appropriate circumstances. It is interesting that the effective dose is that which necrotizes fibrous tissues and that lesser dosage does not do the job.

Dr. Woodburne and others have shown that these lesions usually possess a dense fibrous capsule. Their structure suggests that they represent cystic degeneration in a fibrotic nodule. Since the fibrotic tissue of the nodule undergoes myxomatous degeneration productive of a substance like synovial fluid, one may surmise that this mesodermal tissue is of synovial nature or potentiality, improperly located.

Savatard, in 1924, illustrated the fibrotic nodule of which I speak. The paper of MacKee and Andrews, of 1922, was the source of Sutton's illustration 539 in the tenth edition of "Diseases of the Skin." This illustration shows clearly the fibrotic capsule within which degeneration has occurred.

But in figure 536 of this text is shown what was clinically a typical synovial lesion; yet a multicellular epithelioid lining was present, and the lesion was interpreted by W. F. Harvey, of the Royal College of Physicians Laboratory in Edinburgh, as synovial endothelioma.

Of some 56 cases of Dr. Woodburne—38 of the wrist, 10 of the hand, 4 of the fingers and 4 of the ankles—the lesions of the fingers apparently are in the minority. I am not sure that all clinically similar so-called synovial lesions of the fingers represent, in fact, the same pathologic process, nor am I certain that ganglions of the wrist and elsewhere are identical with the lesions of the fingers, for synovial sarcoma is not excessively rare as a complication of synoviomas near large joints, while sarcoma from the lesions of the fingers has, so far as I know, never been reported.

DR. GEORGE C. ANDREWS, New York: I think that we are all in agreement, in the first place, that these lesions result from a myxomatous degeneration of fibrous tissue. Whether that fibrous tissue comes first as a fibroma and then degenerates or whether it does not come that way is a matter which has not been decided.

The point that these lesions usually occur in middle-aged persons, often in persons who have enlargements of the joints due to arthritis, is worth mentioning. As Dr. Sutton says, there may be a connection with the synovial membrane in these lesions, even though they are not definitely proved to be synovial cysts. I have for several years called them periarticular fibromas which have undergone myxomatous degeneration, on the advice of a well known pathologist who has studied the subject.

When these lesions are dissected carefully, one can frequently demonstrate a fibrous cord connecting the lesion with the capsule of the underlying articulation. I think that one point in Dr. Woodburne's paper which is important for us to remember is that they are usually multiple. It is important to tell the patient of this fact if one is going to give surgical treatment. One may cut out the lesion and another may come.

Another point is that from treatment with injections immobility of the joint may result.

As to treatment with roentgen rays, I have periods in which I am enthusiastic about it and other periods in which I feel as Dr. Templeton does. I think that the dosage which has been most successful, in my experience, is that advised by Dr. Woodburne—fairly high voltage with filtration and fairly large doses, repeated two or three times.

DR. FRED WISE, New York: I wish that Dr. Woodburne, in closing, would give us a general idea of the response to roentgen ray therapy of the different methods which he described with respect to lesions the size of a pea, let us say, on the index finger and a dollar-sized lesion on the flexor surface of the wrist. It seems to me that there must be a great difference in response in lesions varying in size, and I should like to know whether he changes his technic and his filtration, depending on the size of the lesion.

DR. GEORGE M. MACKEE, New York: It is perhaps unfortunate that the method of election for the treatment of these lesions is with roentgen rays, particularly because the dose must be a reactive one. I can detect an element of danger there, which I think Dr. Woodburne also recognizes, because a dose of that quantity, as he states, does leave a defect caused by the irradiation—in other words, chronic radiodermatitis.

In a certain proportion of patients who are young enough to have an expectancy of life of ten or fifteen years epithelioma will develop. Of course, the area is small, which means less danger than would be the case with a larger area.

The plastic surgeons and cancer specialists are busy excising chronic radio-dermatitis, with the danger potentiality of about 25 per cent, and also excising carcinomas. Therefore, I think that it is well, when one is dealing with benign lesions, not to call treatment with roentgen rays or radium the method of election unless the curative dose is below the amount that will cause a reaction, because even one site of erythema caused by roentgen rays or radium may have undesirable sequelae ten or fifteen years later.

The value of this article, which is important, is the determination of the pathogenesis and the change in the nomenclature. I wonder if Dr. Woodburne studied the mucous retention cysts in this connection.

DR. HAROLD N. COLE, Cleveland: I enjoyed this paper, but I should like to ask Dr. Woodburne why it is that practically all these lesions are seen on the extremities—on the ankles or toes, but more particularly on the fingers. We do find them, of course, along the tendon sheaths on the wrists, so that I am not sure that there may not have been at some time some connection with the sheath.

To mention another point in treatment, a good many years ago we had 1 of these patients, a woman who was dissatisfied with the roentgen ray therapy which we had given her, and I sent her to a surgeon friend. He suggested a simple measure that worked in her case, and we have used it, I should say, in 50 per cent of patients with these lesions on the fingers. All that is necessary is the application of a splint and putting the hand at rest. If they will do this for a month or two, 50 per cent of the lesions will go away. I suggest simply that they use it in the daytime.

DR. LLOYD W. KETRON, Baltimore: I have also had some favorable results in treating these cysts in a manner similar to that used by Dr. Cole. The lesion was incised, the contents removed and the inside of the wall wiped out with pure phenol. A tight bandage was then applied with adhesive tape and left on for two or three weeks. I should also like to back up Dr. MacKee's warning about the use of such large doses of roentgen rays in such benign lesions. It is likely that there may be serious radiation sequelae.

I should like to ask Dr. Woodburne one question: How can one explain the fact that these synovial cysts fill up so quickly after their contents are removed if they are due to myxomatous degeneration of the fibrous tissues?

DR. EARL D. OSBORNE, Buffalo: I should like to call attention to one little trick in the treatment of these lesions. Some years ago, in desperation, in treating a recurrent lesion on a patient's finger, I had to do something for it. It had been operated on a number of times with resultant scarring. I told her to put a piece of adhesive plaster around her finger as tightly as she could, without shutting off the blood supply. I saw her four weeks later, and the lesion was gone.

Since then, I have employed this pressure treatment in a number of cases, and in 40 or 50 per cent of them the lesion disappears, not to return. A minimum of eight weeks should be allowed. Pressure treatment should be used postoperatively, after destruction by electrothermic means.

DR. MARTIN T. VAN STUDDIFORD, New Orleans: This borders on a little work which my colleagues and I have been doing in treating birthmarks and cysts with rubber pressure bandages. Later on, I want to read a paper on that—I won't tell you too much about it—but we use a rubber sponge, and on 2 or 3

## WOODBURN—MYXOMATOUS DEGENERATION CISTS

patients with lesions too large for treatment with radium or roentgen rays, we have used rubber pressure bandages. We have cut kneeing pads into pieces of the proper size, left them on for three to five weeks sometimes and had satisfactory results.

DR. JAMES R. DRIVER, Cleveland: I should like to emphasize what Dr. MacKee said in regard to irradiation in these cases. Several years ago Dr. Cole and I had a patient with one of these lesions on a finger. We treated it with roentgen rays, as I recall now 1,000 r, unfiltered, and 100 kilovolts through a small window. Erythema developed, and there developed secondary infection which extended into the tendon sheath, and amputation of the finger was necessary.

DR. GEORGE M. MACKEE, New York: Apropos of the pressure treatment, the last case of synovial lesion that I saw was under the finger nail. It caused considerable pain because of the pressure. Relief was obtained by using a dental drill through the nail and into the cyst and emptying the cyst, thus relieving the pressure.

The point is that there was pressure, produced by the nail, and the cyst developed anyway, and it recurred after it was emptied.

DR. FRED D. WEIDMAN, Philadelphia: Dr. Woodburne has touched off a rich discussion this morning which contains several items that collectively bear on the pathologic changes in the disease.

To begin with, the composition of the lymphatic fluid is highly variable in different parts of the body. Admittedly, synovial fluid and the fluid of the tendon sheaths is a modified lymphatic fluid, and the tendon sheaths lie close to these degeneration cysts. This would mean that there are possibilities for seepage, if not actual rupture of a tendon sheath and the escape of the fluid into the tissues nearby. In that event, the fluid in such situations would be of the order of edema, but the special form of edema connoted by its origin in the tendon sheath.

Now, in order that there shall be a special composition of the fluid in the tendon sheaths, there must be some modifying effects on the part of the cells lining these sheaths (a special metabolic function), and perhaps, inasmuch as there is a common embryologic origin for the connective tissue of the sheath lining and the fibrous tissue round about, the cells of the latter have become improperly differentiated in such a way that they modify the composition of the surrounding edematous fluid.

The observation by Dr. Andrews of a fibrous cord extending from the region of the tendon to these nodules is, I think, encouraging to such a thesis: that there are more highly differentiated cells in the neighborhood of the tendon and that when influences arise (continuous trauma, for example) leading to hyperactivity of the extopic tendon sheath cells the fluid produced is not the ordinary watery edematous one, but one which partakes more of the qualities of the fluid in the tendon sheaths. I realize that this is purely hypothesis.

Incidentally, more attention is being paid to diseases of connective tissues. In the past, it was the diseases of parenchymatous tissues that received the most study, but I think that all of us are aware that of late the degenerative diseases are receiving their due. Fibrosis is an example in point. It is incumbent on dermatologists to inquire in the future as to whether there are additional expressions of generalized fibrous degenerative diseases in other parts of the body, such as fibrosing arthritis, disease of the intervertebral disks and lesions of that order.

DR. ARTHUR R. WOODBURN, Denver: I want to thank you for a generous discussion.

From my experience, I will have to disagree with the point that Dr. Andrews made about the fibrous tissue cord. I was not able to find fibrous tissue cords in the material which was dissected for me by Dr. Denham and some of our surgical friends in the Army. I could find no regular association between joints or synovial sheaths with these nodules. I think that some other observers have recently made that point in the surgical literature.

I agree entirely with Dr. MacKee, and I tried to make my observations conservative and cautioned of the dangers of resulting radiodermatitis. However, in these patients whose disease does not respond to simpler methods and who are having symptoms, I think that probably the roentgen ray therapy is at times justified.

Dr. Wise commented on the change in the amount of the dosage. Of course, in larger lesions, with the dosage that I mentioned, there will be a more decided reaction than there will be in the smaller lesions. However, it was my observation that greater reaction was usually needed to get a satisfactory result.

fatty acids on a large series of patients with recurrent vesicular dermatitis of the hands have confirmed these earlier observations.

In the second paper<sup>5</sup> of this series it was shown that fatty acids are more irritating when they are held on an area of skin of which the surface  $\rho\text{H}$  is increased by the frequent addition of a buffer solution. This is probably the equivalent of converting some of the fatty acid to a soap. At the time that paper was written the hypothesis was stated that while fatty acids of low molecular weight, such as lauric acid, are irritating to the skin at a low  $\rho\text{H}$ , the acids of high molecular weight, such as stearic acid, would become irritating only if the cutaneous surface with which the fatty acid is in contact were maintained either at a relatively high  $\rho\text{H}$  or possibly at not so high a  $\rho\text{H}$  for a longer period of time. The work of other investigators and our own work reported in this paper support this hypothesis.

A patch test with a sodium soap of a fatty acid is somewhat the equivalent of a patch test with a fatty acid at an elevated  $\rho\text{H}$ , since the soaps are, of course, more alkaline than the fatty acids themselves. Emery and Edwards<sup>6</sup> have shown that among the sodium soaps of the saturated fatty acids, sodium laurate gives the highest percentage of positive reactions to patch tests. They also showed that the sodium soap of oleic acid, an unsaturated acid, elicited more positive reactions to patch tests than the sodium soap of stearic acid, the corresponding C<sub>18</sub> saturated fatty acid.

The results of comparable patch tests with the sodium soaps of the chemically pure fatty acids on a large series of patients with recurrent vesicular dermatitis of the hands have been observed by us. Our tests were made in the following manner. A piece of white canton flannel, about 4 mm. square, is fastened to the center of a piece of non-moisture-proof cellophane, about 18 mm. square, with a drop of flexible collodion. A series of these squares is then put onto a 4 cm. strip of adhesive tape. The cloth square is then moistened with a drop of distilled water, and with the moistened tip of a wooden applicator a small piece of the dry sodium soap of a single fatty acid is transferred to the moistened cloth. The adhesive strip, which has one square for each substance to which the patient is being tested, is fastened around the arm, only the inner aspect of the arm being used when the strip is not too long. The strip is held in place more securely if a gauze bandage 2 inches (5 cm.) wide is used over it. This remains on the arm for twenty-four hours and the result is read one hour after it is removed.

5. Blank, I. H.: Action of Soap on Skin: II. Patch Tests with Fatty Acids at Various Hydrogen Ion Concentrations, *Arch. Dermat. & Syph.* **39**:817-821 (May) 1939.

6. Emery, B. E., and Edwards, L. D.: The Pharmacology of Soaps: II. The Irritant Action of Soaps on Human Skin, *J. Am. Pharm. A. (Scient. Ed.)*, **29**:251-254 (June) 1940.

mild erythema and the stearic acid almost always a negative reaction. The results of a test of this type are shown in figure 2.

Thus, it is apparent that even though a fatty acid of low molecular weight, such as lauric, may be irritating to the skin at a  $pH$  of 7 or lower, the fatty acids of higher molecular weight (palmitic and stearic) will probably not irritate the skin even at a  $pH$  as high as 9.

As previously stated, a cake of soap made from palmitic and stearic acid (this mixture is commercially called triple-pressed stearic acid) at a  $pH$  of 9 would be an unsatisfactory detergent. It would be hard, would

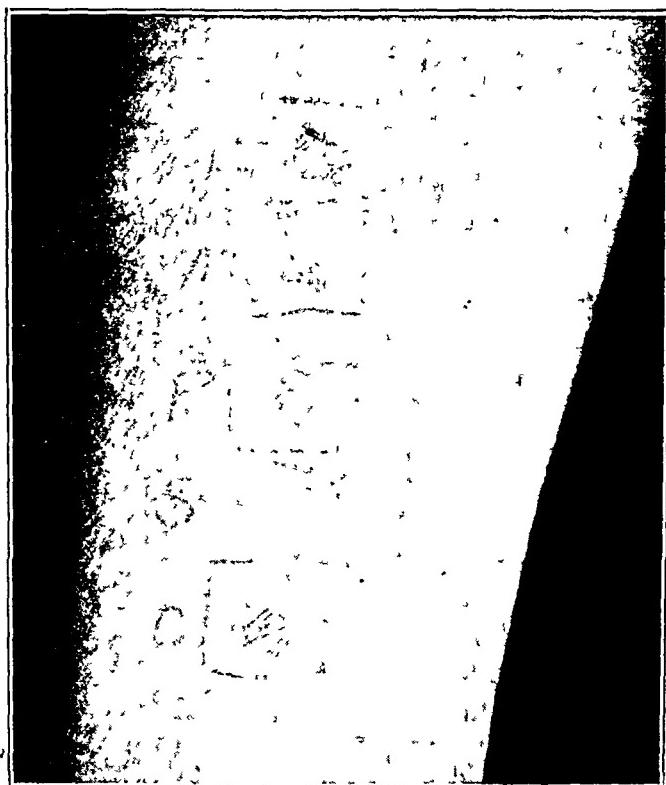


Fig. 1.—Reactions to patch tests with the sodium soaps of lauric, myristic, palmitic, stearic and oleic acids.

not lather and would clean poorly. If, however, a nonirritating cleansing agent could be added to such a base, a satisfactory detergent might result.

Oleic acid may be sulfated to varying degrees. A series of patch tests with low sulfated oleic acid (9 per cent organic sulfur trioxide) and high sulfated oleic acid (16 per cent organic sulfur trioxide) showed that the higher sulfated material was less irritating to the skin than the low sulfated acid. In a further investigation the low sulfated acid was fractionated into a high sulfated fraction and an unsulfated fraction. Patch tests with these two fractions again showed the high sulfated oleic acid to be nonirritating, while the unsulfated fraction showed many

mended by Kooyman and Snyder,<sup>9</sup> almost never elicited even the mild erythema or wrinkling of the skin not uncommonly resulting with an average toilet soap in tests with this same method.

Clinical investigation of this detergent has been limited primarily to its use by over 200 patients with recurrent vesicular dermatitis of the hands. A regular soap is usually thought to aggravate this type of dermatitis. These patients have used the detergent as a general cleanser for all personal hygiene. They have been asked to avoid the use of other soaps while using this detergent. Other types of treatment, such as with boric acid soaks and mild ointments, usually accompanied this change in detergents.

In no instance, have we seen an exacerbation of the dermatitis which could be interpreted as an irritation or acquired hypersensitivity to the detergent. Almost all the patients found it a satisfactory cleanser. Some patients reported that this detergent caused more smarting than regular soap, and others reported less smarting. There has been no consistent impression as to whether the use of this detergent seems to leave the skin "drier" or "oilier." Until a more satisfactory method for the objective evaluation of "oiliness" of the skin is developed, we are forced to rely on the patients' impressions for such an evaluation, and these impressions are not always reliable. Clinical investigations of the use of this detergent for various cutaneous diseases are being continued by us and other dermatologists.

#### SUMMARY

1. Among the sodium soaps of the single fatty acids commonly contained in soaps (lauric, myristic, palmitic, stearic and oleic), only sodium stearate and sodium palmitate elicit a relatively low percentage of significantly positive reactions to patch tests.
2. Stearic acid and palmitic acid usually elicit a negative reaction when held on the skin in the presence of a buffer solution of pH 9.
3. Highly sulfated oleic acid (sulfato-octadecanoic acid) usually elicits a negative reaction to a patch test.
4. A solid lathering cake detergent made primarily from stearic, palmitic and sulfato-octadecanoic acids and containing little or no lauric or oleic acid has been observed to be nonirritating to the skin both by patch tests and by clinical investigations.

416 Marlborough Street.

9. Kooyman, D. J., and Snyder, F. H.: Tests for Mildness of Soap, Arch. Dermat. & Syph. 46:846-855 (Dec.) 1942.

a hereditary tendency, illustrated by occurrence of 2 of his cases in brother and sister.

From histologic studies made on several of the lesions Mibelli stated that the disease began as acanthosis of the surface epithelium, accompanied with hyperkeratosis. In an advanced stage, the hyperkeratosis stopped and there was an atrophy of the prickle cell layer through pressure of the already formed keratosis. In these places the hair follicles and sebaceous glands were absent. The process affected chiefly the sweat gland pores, which were filled with a horny black layer. The center of the duct projected like a plume. It was by coalescence of a number of these plugs that the ridge was formed. In the cutis there was some dilatation of the vessels of the papillary and subpapillary parts. There was an infiltration of lymphoid cells about the walls of the vessels. In no place was there migration of these cells into the interspinous spaces of the prickle cell layer.

Respighi reported almost simultaneously a group of 7 cases, which in a clinical and pathologic sense were the same as those described by Mibelli. He observed that the nails were secondarily affected and described them as cloudy, brittle and falling off easily. Spots were seen on the palms and soles. The histologic structure in these cases followed closely that in the cases of Mibelli, but more stress was laid on the involvement of the follicles with horny plugs, which penetrated almost to the acini. It was his idea that there was parasitic hyperkeratosis or parakeratosis of the mouths of the tubular and acinous glands.

In 1898 Ducrey and Respighi<sup>3</sup> published a detailed study of 11 cases. They showed that the mucous membrane as well as the skin could be involved. All parts of the buccal mucous membrane could be affected, and lesions could be recognized even if cutaneous lesions were absent.

Hutchins,<sup>4</sup> of Atlanta, Ga., was the first to report a case of porokeratosis in America, in 1896. His patient had been under observation since 1892, and he recognized the disease as porokeratosis as described by Mibelli after reading his report. The disease began in his patient at the age of 2 years as a seed-wart-like growth just inside the border of the left palm at the radial side of the base of the index

3. Ducrey, A., and Respighi, E.: The Localization on the Buccal Mucous Membranes of the Affection Improperly Called Porokeratosis: Preliminary Note, Ann. de dermat. et syph. **9**:1, 1898; abstracted, J. Cutan. & Genito-Urin. Dis. **16**:545, 1898; Hyperkeratosis Figurata Centrifuga Atrophicans, Improperly Called Porokeratosis: A Peculiar Skin Affection with Localization upon the Skin and Mucous Membrane; a New Clinical and Histological Study, Ann. de dermat. et syph. **9**:609 and 734, 1898; abstracted, J. Cutan. & Genito-Urin. Dis. **16**:546, 1898.

4. Hutchins, M. B.: A Case of Porokeratosis Mibelli, J. Cutan. & Genito-Urin. Dis. **14**:373, 1896.

finger and spread peripherally. In 1896, when the patient was 32 years old, he had lesions on the left palm, the back of the hand, the forearm and the face.

Although Hutchins was the first to report a case in this country, Stelwagon<sup>5</sup> in his treatise on dermatology told of a case seen by him in 1887, the true nature of which he did not recognize until some years later.

The second report to be published in this country was that of Gilchrist<sup>6</sup> in 1897. He reported 11 cases in which it was thought that the disease had followed a course of transmission from grandmother

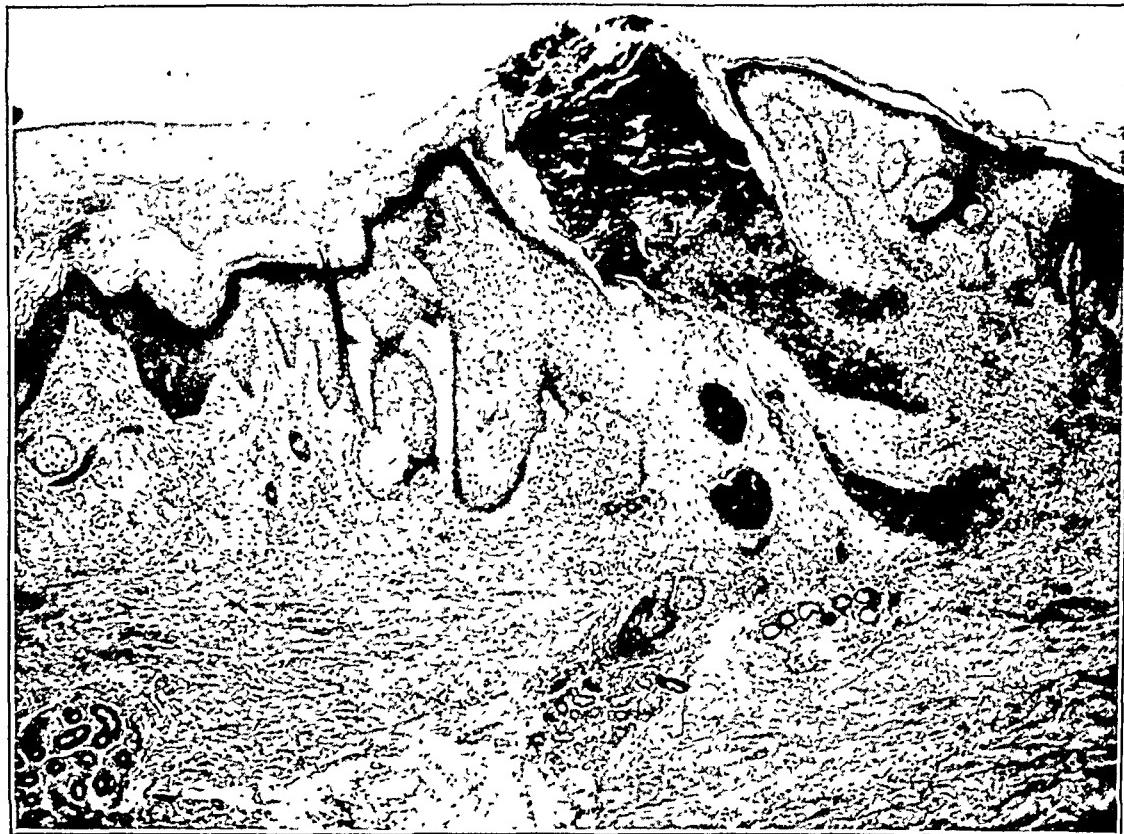


Fig. 1.—Typical follicular plugging, moderate hyperkeratosis and acanthosis. Perivascular infiltration in the corium, with newly formed connective tissue in the papillae.

to grandchildren. In 1899 Gilchrist wrote a complete clinical and histologic description of the 11 cases which he had briefly reported in 1897.

5. Stelwagon, H. W.: A Treatise on Diseases of the Skin, ed. 9, Philadelphia, W. B. Saunders Company, 1923.

6. Gilchrist, T. C.: Eleven Cases of Porokeratosis (Mibelli) in One Family, *J. Cutan. & Genito-Urin. Dis.* **17**:149, 1899; A Case of Porokeratosis (Mibelli) or Hyperkeratosis Excentrica (Respighi) with a Remarkable Family History, *Bull. Johns Hopkins Hosp.* **8**:107, 1897.

In June 1897 Joseph<sup>7</sup> gave an exhaustive account of 2 cases which he had encountered in Germany. The following year, 1898, Wende<sup>8</sup> reported the next case occurring in America. Efforts to determine a possible infectious origin of this disease were unsuccessful.

A case reported by Basch<sup>9</sup> in 1898 presented characteristic lesions. After histologic study of these lesions the author agreed that the disease originated in the sweat glands and especially in their epidermal portion. Bacteriologic examinations in this case revealed nothing of significance.

Mibelli in 1899 reported another case in which lesions were observed on the glans penis and in the mouth in a patient 68 years old. The disease was of thirty years' duration and occupied the trunk and both extremities. It was traceable through four generations.

Between 1900 and 1905 there was little reported in the literature concerning porokeratosis. In 1905 Mibelli reported 2 new cases. Truffi<sup>10</sup> in 1905 presented a case in a boy of 13, in whom the lesions had been present since 11 months of age. In 1907 Himmel and Brocq and Pautier<sup>11</sup> reported cases, and in 1908 Baum<sup>12</sup> saw a patient with lesions distributed along the nerve trunk. Isaac<sup>13</sup> presented a case in 1913 in which only the scrotum was involved. Maki<sup>14</sup> reported in 1914 3 cases of porokeratosis. Sellei<sup>15</sup> in 1914 reported a case in a man who had lesions on the palms and soles. In 1916 Matsumoto<sup>16</sup> described a single case, and in 1918 he made a detailed report of 13 cases. MacCormac and Pellier<sup>17</sup> reported a case in 1918. Other cases were reported by Sevenig in 1918, Harris<sup>18</sup> in 1919 and Bruck and Hirsch<sup>19</sup> and Bukovsky<sup>20</sup> in 1920. An excellent review of the literature with

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- 7. Joseph, M.: Ueber Porokeratosis, Arch. f. Dermat. u. Syph. **39**:334, 1897.
  - 8. Wende, G. W.: Porokeratosis with Report of a Case, J. Cutan. & Genito-Urin. Dis. **16**:505, 1898.
  - 9. Basch, E.: A Case of Porokeratosis (Mibelli), Pest. med.-chir. presse **34**:625, 1898; abstracted, J. Cutan. & Genito-Urin. Dis. **16**:547, 1898.
  - 10. Truffi, M.: Sur un cas de porokératose systématisée, Ann. de dermat et syph. **6**:521, 1905.
  - 11. Himmel, cited by Wright,<sup>21</sup> and Brocq and Pautier, cited by Wright.<sup>21</sup>
  - 12. Baum, cited by Wright.<sup>21</sup>
  - 13. Isaac, cited by Wright.<sup>21</sup>
  - 14. Maki, G.: Three Interesting Cases of Porokeratosis and Its Treatment, Jap. Ztschr. f. Dermat. u. Urol. **14**:223, 1941; abstracted, J. Cutan. Dis. **32**:530, 1914.
  - 15. Sellei, cited by Wright.<sup>21</sup>
  - 16. Matsumoto, S. I.: A Peculiar Form of Porokeratosis, J. Cutan. Dis. **34**:489, 1916; The So-Called Porokeratosis (Mibelli) with Special Reference to Its Histopathology, ibid. **36**:379, 1918.
  - 17. MacCormac, H., and Pellier, C. de C.: A Case of Porokeratosis, Brit. J. Dermat. **30**:197, 1918.
  - 18. Harris, A.: Porokeratosis, J. Cutan. Dis. **37**:56, 1919.
  - 19. Bruck, W., and Hirsch, H.: Ueber Porokeratosis, Dermat. Ztschr. **29**:223, 1920; abstracted, Arch. Dermat. & Syph. **2**:393 (Sept.) 1920.
  - 20. Bukovsky, J.: Hyperkeratosis Eccentrica, Česká dermat. **2**:61, 1920; abstracted, Arch. Dermat. & Syph. **4**:246 (Aug.) 1921.

the report of a case was made by Wright<sup>21</sup> in 1921. A case occurring in a 16 month old baby was reported in 1921 by Scholl.<sup>22</sup> Foerster<sup>23</sup> and Milian and Lefèvre<sup>24</sup> reported cases in 1922.

This disease, considered rare in France, was reported by Louste, Thibaut and G. Barbier<sup>25</sup> in 1923. Other cases were presented in 1923 by Wile,<sup>26</sup> Finnerud,<sup>27</sup> Gregor<sup>28</sup> and Fulde,<sup>29</sup> by Hodara and Behdjet<sup>30</sup> in 1924 and by Acton<sup>31</sup> in 1927.

Hall<sup>32</sup> described the occurrence of 6 cases of porokeratosis in Chinese patients. Lain<sup>33</sup> in 1928 presented 3 cases in one family. Lewin<sup>34</sup> and Ichteiman<sup>35</sup> reported cases in 1931. A complete review of the literature with an extensive bibliography was published by Moncorps<sup>36</sup> in 1931.

Ritchie and Becker<sup>37</sup> inoculated animals with tissue taken from their patient in an effort to prove an infectious origin. Several typical cases



Fig. 2.—Cross section of small lesion, showing acanthosis with follicular plugging at either end of the section and moderate inflammatory infiltration of corium. Sweat glands are present and normal in appearance.

- 21. Wright, C. S.: Porokeratosis: Report of a Case, *Arch. Dermat. & Syph.* **4**:469 (Oct.) 1921.
- 22. Scholl, O. K.: A Case of Porokeratosis Limited to One Side of the Body; *Dermat. Wchnschr.* **72**:1, 1921; abstracted, *Arch. Dermat. & Syph.* **4**:394 (Sept.) 1921.
- 23. Foerster, O. H.: Porokeratosis (Mibelli), *Arch. Dermat. & Syph.* **5**:796 (June) 1922.
- 24. Milian and Lefèvre: Porokeratosis of Mibelli, *Bull. Soc. franç. de dermat. et syph.* **29**:41, 1922; abstracted, *Arch. Dermat. & Syph.* **6**:206 (Aug.) 1922.
- 25. Louste, Thibaut and Barbier, G.: Porokeratosis of Mibelli, *Bull. Soc. franç. de dermat. et syph.* **30**:252, 1923; abstracted, *Arch. Dermat. & Syph.* **8**:716 (Nov.) 1923.
- 26. Wile, J.: Porokeratosis, *Arch. Dermat. & Syph.* **8**:869 (Dec.) 1923.
- 27. Finnerud, F.: Porokeratosis, *Arch. Dermat. & Syph.* **7**:708 (May) 1923.
- 28. Gregor, F. W.: Porokeratosis, *Indiana M. A. J.* **16**:274, 1923.
- 29. Fulde, E.: Studien über Vererbung von Hautkrankheiten: IV. Porokeratosis Mibelli, *Arch. f. Dermat. u. Syph.* **114**:6, 1923.

were described from 1932 to 1934 by Thompson,<sup>38</sup> Verrotti,<sup>39</sup> Kobayasi<sup>40</sup> and Kauczynski.<sup>41</sup> Ambler and Stout<sup>42</sup> in 1934 presented a case of porokeratosis occurring in a Negro. Only 2 other instances had been mentioned previously in which this disease was recognized in Negroes, 1 by Hutchins<sup>4</sup> and the other by Tauber<sup>43</sup> in his discussion of the case reported by Ambler. Reports of cases were published by Shiller,<sup>44</sup> Gross,<sup>45</sup> and Andrews<sup>46</sup> in 1937.

- 30. Hodara, M., and Behdjet, H.: Histologic Investigation of a Case of Porokeratosis of Mibelli, *Dermat. Wchnschr.* **77**:1168, 1923; abstracted, *Arch. Dermat. & Syph.* **9**:760 (June) 1924; A Second Case of Porokeratosis of Mibelli, *Dermat. Wchnschr.* **77**:1167, 1923; abstracted, *Arch. Dermat. & Syph.* **8**:760 (June) 1924.
- 31. Acton, H. W.: Porokeratosis: Its Causation and Treatment, *Indian J. M. Research* **15**:349, 1927.
- 32. Hall, G. A. M.: Porokeratosis (Mibelli): Report of Its Occurrence in Six Chinese Patients, *Arch. Dermat. & Syph.* **18**:396 (Sept.) 1928.
- 33. Lain, E. S.: Porokeratosis: Report of Three Cases, *Urol. & Cutan. Rev.* **32**:383, 1928.
- 34. Lewin, L.: A Case of Porokeratosis Mibelli, *Sovet. vestnik dermat.* **9**:176, 1931; abstracted, *Arch. Dermat. & Syph.* **24**:1091 (Dec.) 1931.
- 35. Ichteiman, M. S.: Clinical and Histologic Study of Porokeratosis Mibelli, *Sovet. vestnik dermat.* **9**:674, 1931; abstracted, *Arch. Dermat. & Syph.* **26**:517 (Sept.) 1932.
- 36. Moncorps, C.: Porokeratosis Mibelli, in Jadassohn, J.: *Handbuch der Haut- und Geschlechtskrankheiten*, Berlin, Julius Springer, 1931, vol. 8, pt. 2, pp. 463-481.
- 37. Ritchie, E. B., and Becker, W. E.: Porokeratosis (Mibelli): Report of a Case; Histologic Study and Animal Inoculation, *Arch. Dermat. & Syph.* **26**:1032 (Dec.) 1932.
- 38. Thompson, M. S.: A Case of Porokeratosis of Mibelli, *Brit. J. Dermat.* **44**:544, 1932.
- 39. Verrotti, G.: A Peculiar Case of Porokeratosis Mibelli with Corneomas, *Gior. Ital. di dermat.* **74**:3, 1933; abstracted, *Arch. Dermat. & Syph.* **28**:572 (Oct.) 1933.
- 40. Kobayasi, T.: Generalized Porokeratosis Mibelli with Lesions of the Buccal Mucosa and of the Nails, *Jap. J. Dermat. & Urol.* **36**:439, 1934; abstracted, *Arch. Dermat. & Syph.* **31**:715 (May) 1935.
- 41. Kauczynski, K.: Porokeratosis Mibelli, *Przegl. dermat.* **29**:294, 1934; abstracted, *Arch. Dermat. & Syph.* **32**:115 (July) 1935.
- 42. Ambler, J. V., and Stout, K. L.: Porokeratosis (Mibelli): A Report of Its Occurrence in a Negro, *Arch. Dermat. & Syph.* **29**:20 (Jan.) 1934.
- 43. Tauber, E. B., in discussion on Ambler, J. V.: Porokeratosis Mibelli, *Arch. Dermat. & Syph.* **25**:1158 (June) 1932.
- 44. Shiller, A. E.: Porokeratosis of Nevous Type, *Arch. Dermat. & Syph.* **35**:1187 (June) 1937.
- 45. Gross, P., and Barker, L. P.: A Case for Diagnosis (Porokeratosis Mibelli), *Arch. Dermat. & Syph.* **36**:179 (July) 1937.
- 46. Andrews, G. C.: Porokeratosis (Mibelli), Disseminated and Superficial Type, *Arch. Dermat. & Syph.* **36**:1111 (Nov.) 1937.

Scholtz,<sup>47</sup> Ayres and Anderson<sup>48</sup> in 1939. Johnson<sup>49</sup> in 1941. Rosen<sup>50</sup> in 1942; and Bloom and Abramowitz<sup>51</sup> and Franks and Davis<sup>51a</sup> in 1943 reported cases.

There has been a great diversity of opinion throughout the literature as to the classification of porokeratosis. It has been generally classified either with the verrucae or the nevi. In favor of the former is the wart-like appearance of the lesions, particularly in the early stages, the histologic picture of hypertrophy of the epidermis and the papillae and the decided hyperkeratosis. The familial tendency, the persistence of the lesions throughout life, the noncontagiousness, the occasional systematic arrangement and the failure to respond to roentgen rays all favor the placing of porokeratosis in the classification of the nevi.

Numerous theories have been proposed by many investigators as to the cause of porokeratosis, but it must still be regarded as a disease of unknown origin. It cannot be denied that heredity plays a part. Cockayne<sup>52</sup> has shown that the method of inheritance is one of regular dominance, since transmission is invariably direct and there is no instance of an apparently normal person's acting as a transmitter. Taking all cases together the proportion of affected males to affected females is 164 to 69, a ratio of more than 2 to 1. Mibelli finally came to the conclusion that porokeratosis could be included with the nevoid dermatoses of a definitely hereditary and familial type and might be described as keratoatrophic nevus. In Truffi's<sup>10</sup> case and a few others the distribution would suggest probably a neurogenous origin, since each group of lesions was mapped out according to the distribution of a peripheral nerve. Attempts to produce an organism or a parasite have failed. No lesions have ever appeared at the site of injection except in Wende's one successful inoculation of his original patient and in the case of Ritchie and Becker, when in one instance they obtained similar microscopic changes in the skin of a guinea pig following the injection of macerated material obtained from a patient with porokeratosis. There

47. Scholtz, J. R.: Porokeratosis (Mibelli), Arch. Dermat. & Syph. **39**:574 (March) 1939.

48. Ayres, S., and Anderson, N. P.: Porokeratosis (Mibelli), Arch. Dermat. & Syph. **39**:574 (March) 1939.

49. Johnson, H. H.: Porokeratosis (Mibelli), Arch. Dermat. & Syph. **43**:574 (March) 1941.

50. Rosen, I.: Porokeratosis Mibelli, Arch. Dermat. & Syph. **45**:782 (April); 982 (May) 1942.

51. Bloom, D., and Abramowitz, E. W.: Porokeratosis Mibelli: Report of Three Cases in One Family, Arch. Dermat. & Syph. **47**:1 (Jan.) 1943.

51a. Franks, A. G., and Davis, M. I. J.: Porokeratosis (Mibelli) Associated with Cutaneous Horn, Dystrophy of Nails and Atrophy of Interosseous Muscles: Report of a Case, Arch. Dermat. & Syph. **48**:50 (July) 1943.

52. Cockayne, E. A.: Inherited Abnormalities of the Skin and Its Appendages, London, Oxford Medical Publications, 1933.

is nothing to recommend a theory of contagion for this disease and much against it. In no case has the wife or the husband of a patient having porokeratosis been affected with the disease. All attempts with inoculation and all attempts to grow an organism on various mediums have been without results; and special stains have shown nothing. Ichteiman<sup>55</sup> expressed the belief that the disease could not be considered nevoid in character and that it belonged to the group of dyskeratoses of Darier. Acton<sup>51</sup> stated the belief that the disease was merely a type of localized hyperkeratosis, with central atrophy and associated with hypofunction of the thyroid gland. He reported complete cures in 3 cases with thyroid therapy.

It has been recognized for a number of years that vitamin A deficiency produces cutaneous abnormalities, characterized by a follicular keratosis or dyskeratosis. The skin with a typical cutaneous eruption from vitamin A deficiency is described as dry and rough, with localized follicular papules containing a central intrafollicular keratotic plug. The plugs frequently project from hair follicles as horny spines. The sweat apparatus is said to be involved in this disease, but to a less extent than the hair follicles and sebaceous glands. The lesions may be generalized or localized, but are usually symmetrically distributed. Some of the first studies on the cutaneous manifestations of vitamin A deficiency were carried out by Frazier and Hu.<sup>53</sup> The principal microscopic observations, as shown by these investigators in their cases of proved vitamin A deficiency, revealed that the pathologic process was primarily hyperkeratinization of the lining epithelium of the hair follicles. Keratosis follicularis has been reported as improved with treatment with vitamin A and has some clinical and microscopic characteristics resembling porokeratosis.

We can demonstrate now that there are certain clinical and histologic characteristics of porokeratosis and vitamin A deficiency which are closely related and suggestive of a common cause. The most consistent cutaneous lesion in these two diseases is a keratotic papule or groups of papules. In porokeratosis the earliest lesion is a single papule with a keratotic surface. In vitamin A deficiency a group of keratotic papules appear either localized or generalized, and they are accompanied with a dry skin and a reduction or absence of sweating. The lesions are usually symmetrically arranged in both diseases.

Histologically these diseases resemble each other in that there is a plugging of the hair follicles and sweat ducts, with a dense mass of cornified cells and hyperkeratosis involving these areas and to a less extent the surrounding tissue. In porokeratosis there is a cellular infiltration of the corium beneath the hyperkeratotic area. In vitamin A

53. Frazier, C. N., and Hu, C. K.: Nature and Distribution According to Age of Cutaneous Manifestations of Vitamin A Deficiency, Arch. Dermat. & Syph. 83:825 (May) 1936.

deficiency there is a moderate lymphocytic infiltration in the area where the sebaceous glands have been damaged or have atrophied. There is also homogenization and sclerosis of the connective tissue. In porokeratosis, beneath the atrophic area the collagen becomes sclerotic and the hair follicles and sebaceous glands and at times the sweat glands disappear.

From the foregoing, we propose the theory of vitamin A deficiency as a causative factor in porokeratosis. We have neither proved nor disproved this theory, but merely present it as a possibility. We have been unable to follow the cases reported in this paper since the idea of vitamin A deficiency was considered and have therefore had no opportunity for putting it to trial.

Mibelli classified this disease as one of the incurable dermatoses. Many and varied treatments have been tried, mostly without success. Total excision or destruction of the lesions by electrocautery has given the best results. There have been reports of recurrence of the lesions at the site of destruction with electrodesiccation or cauterization, but this is the treatment of choice in early stages of the disease. The use of solid carbon dioxide has generally proved unsatisfactory. Roentgen and radium therapy have been unsuccessful. Local treatment with mercury ointments and various keratolytic agents has been valueless. Potassium iodide and compounds of mercury and other heavy metals have been given by mouth without effect. Curettage followed by cauterization of the base of the lesion with silver nitrate or other caustics has been used by many, but frequently results in recurrence of the lesion within a few months.

Acton<sup>31</sup> observed that a high percentage of his patients had a low basal metabolic rate. He treated these patients with a large dose of thyroid extract and reported immediate improvement with cures in two weeks. His work, however, has not been substantiated by other investigators.

#### REPORTS OF CASES

CASE 1.—G. T., an 18 year old white youth who had congenital syphilis with juvenile paresis, was first brought to the University of Virginia Hospital in 1941 when he began to show evidence of mental deterioration. On routine examination the boy was observed to have unusual keratotic lesions on the back of the neck and the right arm. He also had blue scleras and a history of numerous fractures of the legs and arms, and from this a diagnosis of fragilitas ossium was made.

This boy first experienced cutaneous lesions on his neck at the age of 12. The only symptom was slight itching. The lesions on the neck slowly increased in size, and new ones appeared on the right arm, beginning as tiny red papules and extending peripherally in ring formation. No treatment had been tried except for "sulfur and lard" as a home remedy.

The patient was born out of wedlock of a syphilitic mother. There was no history of similar cutaneous lesions in the mother or maternal grandparents. It is not known whether the father or any of his family were affected.

Physical examination revealed a poorly developed, abnormally small and mentally retarded boy who appeared about 10 years of age. There was a moderately severe acne of the face, back and shoulders. There were a few keratotic cutaneous lesions on the neck and forearms. The scleras were blue.

In November 1944 this patient was observed to have eight peculiar cutaneous lesions of various sizes on the neck and both forearms. On the right side of the back of the neck there was a large gyrate lesion about 0.75 by 1.25 inches (about 1.9 by 3.2 cm.) in diameter.

Three lesions were present on the left forearm. These were annular lesions 1 by 0.75 inch (2.5 by 1.9 cm.), 1 by 0.5 inch (2.5 by 1.27 cm.) and 0.5 by 0.5 inch (1.27 by 1.27 cm.) in diameter, respectively. They appeared on the flexor surface, slightly distal to the cubital area and were grouped close together. These lesions also presented a depressed slightly atrophic central area, with a raised hyperkeratotic border composed of closely adherent papules, as described for the other areas. One of the smaller lesions was excised for microscopic examination, and a small keloid developed in this area. On the right forearm were three small



Fig. 3.—Porokeratosis (case 1).

lesions, which had developed in the past year. These lesions consisted of small individual papules with dark rough keratotic tops.

Numerous routine and special laboratory tests were made, without any significant observations. Wassermann and Kahn reactions of the blood were strongly positive. Examination of the spinal fluid showed grade I changes for neurosyphilis.

All the cutaneous lesions originated as single papules, but soon a group of three or four new papules appeared. The lesions spread peripherally, forming an annular plaque with a typical border or keratotic ridge. The center of each lesion became depressed below the surface of the ridge and appeared atrophic. Growth of all these lesions was slow but progressive.

No treatment of the cutaneous lesions was attempted. There has been no recurrence of the lesion that was excised for microscopic examination. The patient received regular antisyphilitic treatment with arsenic and bismuth compounds and fever induced with typhoid vaccine, with no effect on the skin.

The section of skin from the neck was shown by microscopic examination to consist of a rather thick hyperkeratotic plaque, located at a sweat gland opening.

The plugged pore was filled with desquamated squamous cells and a large number of polymorphonuclear leukocytes. The pore could be traced to a sweat gland, and the stratified squamous epithelium in the walls of the pore was greatly thickened because of an increase in the keratinization of the cells. The sweat glands beneath the lesion were distended. The corium in the region of the plaque showed perivascular infiltration with lymphocytes and a few polymorphonuclear leukocytes. There appeared to be considerable newly formed connective tissue in the papillae and also some fibrous proliferation about the sweat glands. Other than slight hyperkeratosis no conspicuous changes were seen in the epidermis adjacent to the plaque.

A second biopsy specimen was taken from a small young lesion on the arm. Microscopic examination of this section revealed a definite localized type of acanthosis with mild hyperkeratosis and a thick stratum granulosum, located so as to involve both sweat pores and follicles. A deep intraepidermal dilated area occurred at one point and was filled with horny material and leukocytes. The sweat glands were numerous. Their ducts were studied by serial sections, but no great changes were evident until the epidermis was reached. In most areas the duct throughout



Fig. 4.—Porokeratosis (case 2)

its progress was normal. Immediately surrounding the epithelium of a dilated pore were macrophages, a few lymphocytes and a few foreign body giant cells. A light inflammatory infiltrate was present in the corium. There was some vascular and connective tissue proliferation in the papillae.

CASE 2.—A white schoolboy, 16 years of age, was seen on Sept. 2, 1943, for treatment of acne of the face and back. During the routine examination two unusual hyperkeratotic lesions were noted on each side of the back of the neck. These lesions had been present three or four years and had produced no symptoms. His local physician had cauterized one area previously, effecting a decrease in its size, but the lesion was still present.

Examination revealed an irregular circinate area about 3 cm. in diameter on the right side of the back of the neck, with a similar but smaller lesion about 2 cm. in diameter, slightly anterior to and below this. On the left side of the neck there was a large semicircular plaque about 3 cm. in diameter, with a smaller annular lesion about 0.75 cm. in diameter and posterior to the larger lesion. The central portion of each lesion showed atrophy of the skin. Surrounding the central atrophic

area was a hyperkeratotic ridge. This was composed of closely arranged tiny conical elevations, some of which had fused to form the ridge. It was reddish brown and had a hard rough surface, forming an incomplete seam on top of the ridge.

The patient refused a biopsy, and no laboratory studies were obtained. He did not return for further examination or treatment.

#### SUMMARY

Porokeratosis is an unusual chronic and progressive cutaneous disease which persists throughout life and is characterized by circinate or oval plaques composed of a hyperkeratotic linear border which progresses peripherally leaving some atrophy at the center. There is a slender furrow running along the center of the peripheral wall from which arises a keratotic ridge.

This disease was first recognized and described by Mibelli in 1893. Since then it has been reported by authors from many countries, including the United States.

The cause remains debatable. That there is a definite hereditary factor has been shown repeatedly by reports of several cases of porokeratosis occurring in one family. Cockayne has shown that the method of inheritance is one of regular dominance, since transmission is invariably direct. Parasitic and infectious origin has been fairly well ruled out by bacteriologic studies and inoculation of animals. The theory that this is a nevoid condition has been favored by many. Hypofunction of the thyroid gland has been suggested as a cause, but has not been substantiated by other investigators. We are, in this paper, suggesting another possible causative factor, which has not been discussed previously. The clinical and histologic observations indicate a possible relationship between porokeratosis and vitamin A deficiency. A brief description of these diseases, pointing out both clinical and histologic similarities, is presented. No investigations have been made to prove this theory, but we offer it as a basis for future study. Until more is known about the physiologic and chemical nature of this disease one should continue to consider it a disease of unknown origin.

Onset of the disease is commonly in childhood, but it may occur any time during adolescence or early adult life. It affects males three times as frequently as females. Porokeratosis should be classed with the incurable dermatoses, since treatment has been unsatisfactory in the majority of cases. Total excision of the lesion is the most reliable means of eliminating the disease but this is suitable only when lesions are small and few.

Two cases of porokeratosis are presented, both occurring in adolescent boys and beginning at about the age of 12, with slow progression of the lesions. In both cases lesions were presented which were clinically typical of the disease. Microscopic sections from 1 of our patients showed characteristic histologic observations of porokeratosis.

## LICHEN PLANUS IN THE NEGRO

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LICHEN planus in the Negro offers a challenge in its clinical diagnosis and interesting histologic characteristics in microscopic examination. Cutaneous eruptions in the Negro have often been clinically masked by the intensive content of melanin. Further, the pigmentation of eruptions in the Negro has often been increased and at other times diminished. Frequently lichen planus has been known to have been followed by vitiligo.

### SUMMARY OF LITERATURE

Fox,<sup>1</sup> in 1910, presented a case of lichen planus in a Negro woman, which early showed large numbers of typical lichen planus papules, but later the typical eruption was replaced by increased pigmentation.

Jacob,<sup>2</sup> in a study of 179 cases of lichen planus in St. Louis, observed only 5 cases in Negroes and stated that Gilchrist, at Johns Hopkins Dispensary in Baltimore, saw only a half-dozen cases in twenty years. He stated that the eruption was typical in every respect except in color. In this respect the dark-skinned persons showed grayish papules.

Jacobson<sup>3</sup> presented a case in a 24 year old Negro man, in which the lesions had become confluent and formed circinate dark brown plaques with smooth depressed centers and elevated ridges, the latter being the color of the patient's normal skin. Frank<sup>4</sup> presented a case of lichen planus in a 5½ year old Negro boy, with a generalized symmetric eruption consisting of violaceous papules.

Hollander and Baer<sup>5</sup> reported a Negro boy aged 12 for whom a diagnosis of lichen planus annularis hypertrophicus had been made.

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From the Division of Dermatology, University of Southern California, Los Angeles, and Los Angeles County General Hospital.

1. Fox, H.: Lichen Planus in a Negress, *J. Cutan. Dis.* **28**:403 (Aug.) 1910.
2. Jacob, F. M.: Some Studies on Lichen Planus, Based on the Study of One Hundred and Seventy-Nine Cases, *Arch. Dermat. & Syph.* **2**:607-616 (Nov.) 1920.
3. Jacobson: Lichen Planus, *Arch. Dermat. & Syph.* **3**:848 (June) 1921.
4. Frank: Lichen Planus in a Colored Child, *Arch. Dermat. & Syph.* **20**:114 (July) 1929.
5. Hollander, and Baer: Lichen Planus Annularis Hypertrophicus, *Arch. Dermat. & Syph.* **17**:439-40 (March) 1928.

In this patient pigmentary changes were evidenced by an especially black center in all the lesions. The lesions on the arms had a lichen shine.

Juliusberg<sup>6</sup> mentioned that lichen planus in the Negro races is rare and that in some cases the papules are darker than the normal skin while in others they vary from a violet hue to gray in dark Negroes.

Appel<sup>7</sup> presented a case in a 40 year old Negro man and stated that he had seen a second case in a Negro woman and speculated that the incidence in Negroes is not so rare as was heretofore believed.

#### CLINICAL APPEARANCE AND CHARACTERISTICS

The clinical appearance of lichen planus in Negroes has many interesting features which are more manifest than those of lichen planus in white persons.

The color, instead of being violaceous red, varies from purplish gray to black. The early lesions are lighter in color and elevated. The late lesions are hyperpigmented. The waxy sheen which is evident early is lost in the late lesions.

The polygonal border of the individual papules is not as acute as in white persons.

#### HISTOLOGY

The microscopic picture of lichen planus in the Negro has rarely been reported.

Early in the disease, hyperkeratosis, increased granulosis and formation of lacunae are present. The pigment normally seen in the numerous layers of the epidermis of Negroes has disappeared. This is especially noticeable in the stratum basale, which is involved by intense colliquative degeneration and is so intense in some areas that small vesicles are formed at the junction of the epidermis and cutis.

Invasion of the epidermis by lymphocytic and polymorphonuclear cells is especially evident at the lower border of the epidermis.

There is a dense cellular infiltration in the papillary cutis, consisting of lymphocytes, polymorphonuclear neutrophils and numerous chromatophores densely packed with pigment.

In late stages the microscopic section shows increased pigmentation in the epidermis, which in early stages was washed out. Atrophy of epidermis is present, recurrence of pigment of the basal layer is observed and heavily pigmented chromatophores persist in the cutis.

6. Juliusberg, F., in Jadassohn, J.: Handbuch der Haut- und Geschlechtskrankheiten, Berlin, Julius Springer, 1931, vol. 7, pt. 2, p. 27.

7. Appel, B.: Lichen Planus Hypertrophicus, Arch. Dermat. & Syph. 53:187 (Feb.) 1946.



Fig. 1.—Early lichen planus lesion in a Negro, showing discoloration.

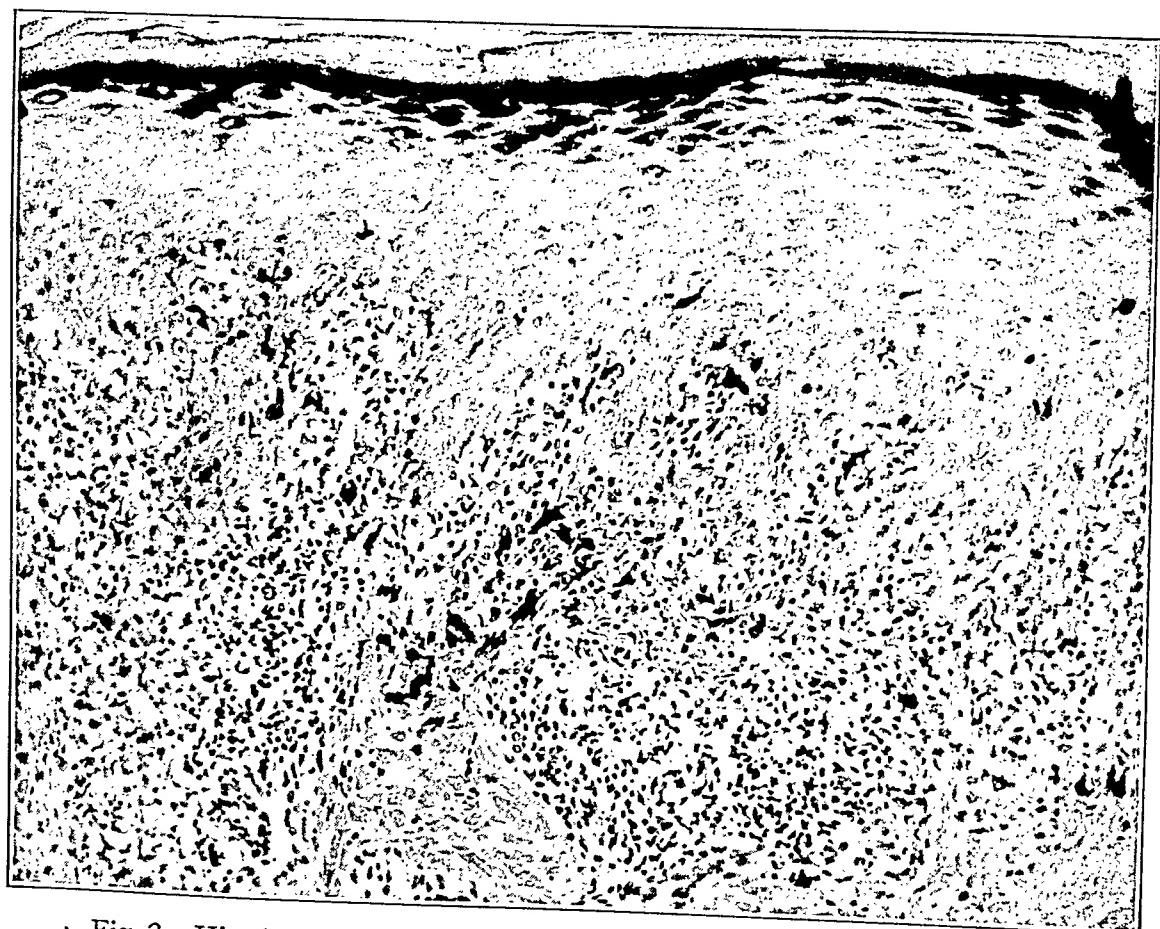


Fig. 2.—Histologic section of a lesion of early lichen planus in a Negro, showing intense granulosis, loss of pigment from basal cells and dense nests of chromatophores in the cutis.

## REPORT OF CASES

CASE 1.—O. L., a 44 year old Negro woman, had a subtotal hysterectomy and appendectomy in July 1945, and at this time she noticed the appearance of "whitish spots" on the inner aspect of her left thigh. These lesions became enlarged and assumed a darker hue. Two to three months later she noticed similar lesions about her abdominal scar and also became aware of lesions in her mouth. The lesions of her thigh and abdominal scar were pruritic.

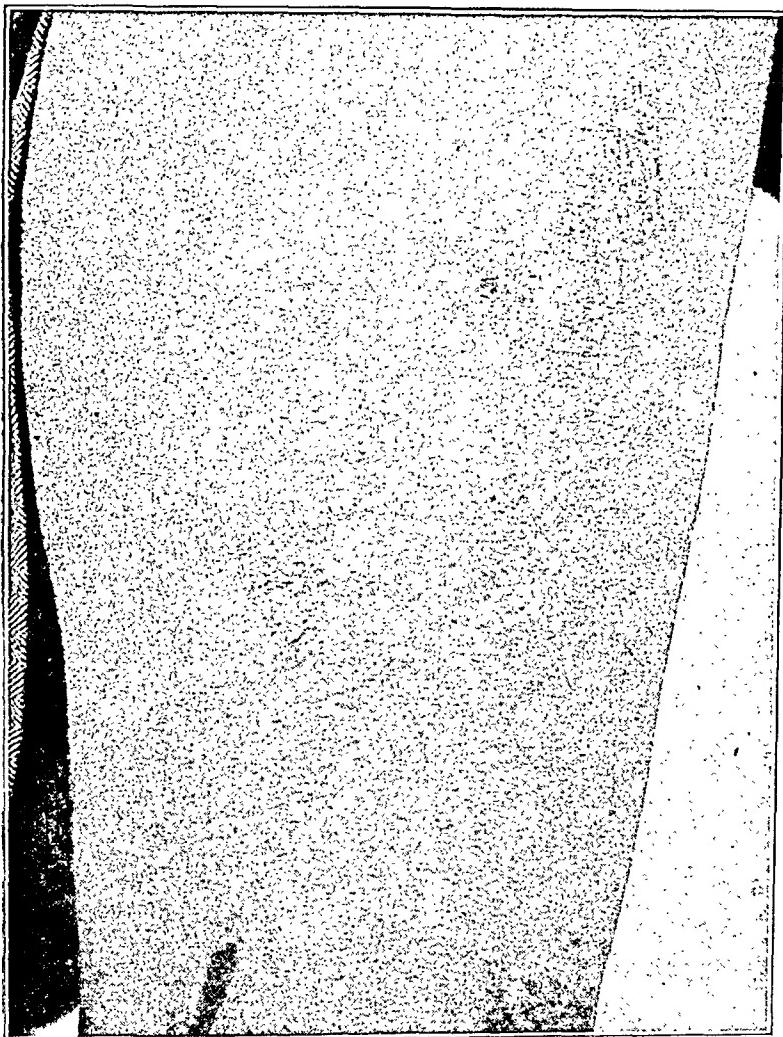


Fig. 3.—Late lichen planus in a Negro, showing hyperpigmentation and absence of discrete borders of papules.

In March 1946 the lesions consisted of 0.5 to 1.5 cm. flat-topped plaques, extending over an area of 3 by 12 cm. on the inner side of the left thigh. There were also a few 0.5 cm. papules about the lower edge of her recent abdominal scar. The lesions were dark brown, irregularly shaped and somewhat shiny. There were reticular whitish plaques, 1 cm. in size, on the mucous membrane of both cheeks.

CASE 2.—L. B., a 49 year old Negro woman, first noticed a reddish papule, 3 mm. in size, on the inner aspect of her left thigh five years before she consulted us.

The lesion gradually increased in size, turned darker and developed satellite lesions which were similar to the original lesion.

Examination in March 1946 revealed a shiny hyperthrophic plaque, 1 by 3.5 cm. in size, on the inner aspect of the left thigh, which was lighter than the heavily pigmented surrounding skin. There were several adjacent papules of pinhead size. No oral lesions were present.



Fig. 4.—Histologic section of a late lesion of lichen planus, showing atrophy of epidermis, recurrence of pigment in the basal cells and dense collections of chromatophores in the cutis.

CASE 3.—R. J. B., a 54 year old Negro, first noticed lesions on his right hip four to five months before we saw him.<sup>8</sup> Lesions then developed on the penis, scrotum, wrists, upper part of the chest and legs. The lesions were nonpruritic.

In May 1946 there was a smooth irregular hyperpigmented plaque, 2 by 4 cm. in size, on the right thigh, which was hyperkeratotic at one edge. On the glans

8. Dr. H. M. Elliot enabled us to study and report this case.

penis there were ring forms, and on the shaft of the penis and on the scrotum were depigmented grayish hyperkeratotic patches, consisting of small papules. The annular plaque on the glans consisted of discrete papules. On the flexor surfaces of the arms were plaques, 1 cm. in size, with depressed hyperpigmented centers and raised lichenified edges. There were hyperpigmented brown spots of healed lesions and also elevated split-pea size bluish new lesions on his chest.

#### COMMENT

We have presented 3 cases of lichen planus occurring in Negroes. The clinical characteristics of depigmentation early in the disease and hyperpigmentation late in the disease are explained by the histologic observations. The grayish lesions are explained by the intense hyperkeratosis, granulosis and loss of pigment from the epidermis. The late black lesions are explained by the recurrence of pigment in the epidermis, the persistence of pigment in the cutis and an atrophy of the epidermis. This disease is not frequently observed in Negroes. Only 17 cases have been previously reported in the literature. We think that this is due not to the rare occurrence in Negroes but rather to either the failure of physicians to make a proper diagnosis, because of the atypical clinical appearance and the infrequency with which biopsies have been made in Negroes, or their failure to report cases observed in Negroes.

#### SUMMARY AND CONCLUSIONS

Three cases of lichen planus in Negroes are presented and the literature is reviewed. Pitfalls of diagnosis of lichen planus in Negroes are commented on.

Depigmentation of lesions early in the disease is due to the colligative degeneration and resultant washing out of pigment from the epidermis. Hyperpigmentation is due to the reformation of epidermal pigment in the atrophic epidermis, the granular layer of which is practically absent.

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ascertain, of this person's unusual growth of hair. Not long afterward several other travelers noted the marvelous length of Chief Long Hair's growth, which was estimated at from 9 feet 11 inches (302 cm.) to 10 feet 7 inches (323 cm.).<sup>2</sup>

My interest in the subject began at a dinner of the Order of Indian Wars of the United States on Feb. 17, 1934, at which the late General Hugh L. Scott, former Chief of Staff, United States Army, and an authority on certain Indian matters, spoke and included in his talk the story of his experiences among the Crow Indians.

General Scott's remarks, according to my notes taken then, were, in part, as follows:

There was formerly a Crow chief called Long Hair on account of his remarkable growth. He wore his hair in a bag suspended from his neck. When he wished to have it brushed he went into his lodge, took it down and spread it out evenly from his head. Other Indians were brought in, sat around the edges of the lodge and combed the hair with porcupine tails. They oiled it, stroked it, then folded it toward the head and finally replaced it in the bag.

The chief died before General Scott visited the Crows, but Scott heard about him from them. He was curious about the matter but never could see any of the hair, although there were vague reports of its still existing as strands in possession of some of the Indians. It was much venerated, as the unusual growth was thought to be a sign of divinity or, at least, to possess supernatural power. The Indians were closemouthed about it. Finally General Scott heard that an Indian named Rabbit Foot had had some of it in his possession, but he, also, was dead. The hair had been buried with him. He then learned that a brave named Plenty Coups was in possession of a strand but was very secretive and easily alarmed about it if the matter was mentioned. They talked together frequently, but the general never once mentioned "hair." Had he done so that blunder would have ended the quest.

General Scott gave up all hope of ever seeing the lock. Twenty years passed. Then, in 1930, together with Mr. Scott Leavitt, chairman of the House of Representatives Committee on Indian Affairs, he was again at the Crow agency. He called on Plenty Coups and had a friendly visit. Again, there was no "hair talk." The next day he was engaged in a ceremonial visit with some other Indians when Plenty Coups came to him and invited him to come to his house the next day, saying that he would show him the hair and anything else he wished to see. He apologized for the visit of the day before and said that his lodge had not been arranged then but that now all was ready. He also invited Mr. Leavitt and a few Indian interpreters.

Mr. Leavitt<sup>3</sup> recently wrote me his version of the visit, which closely corresponded to General Scott's story. Combined into one narrative the account runs about as follows:

On Sept. 22, 1930, the general and the congressman visited Plenty Coups at Crow Agency, Montana. The old chief had an upper chamber in his lodge

2. Lowie, R. H.: The Material Culture of the Crow Indians, Anthrop. Papers Museum Nat. Hist. **21** (pt. 3):228, 1922.

3. Leavitt, S.: Personal communication to the author, Nov. 1, 1944.

where he kept his "medicine bundle" and other objects sacred to him. Besides the persons already mentioned, the interpreter, Max Bigman, an Indian woman and a blind Indian were present. Plenty Coups uttered a ceremonial prayer, bathed his hands, breast and arms in the smoke of a pine needle fire and rubbed his hands with beaver musk. The musk was passed around the circle of visitors preliminary to the production of the hair, which was wrapped in the form of an open circle in cloths of many colors and, finally, in buckskin. Each layer was peeled off until the lock was exposed.

Plenty Coups unwound it slowly and with the utmost reverence, letting it pass from hand to hand around the silent circle, and, as it was unrolled, Max Bigman measured it, hand over hand, for 76 hands<sup>4</sup> 1 finger (about 792 cm.). The general asked Plenty Coups whether the hair was spliced, and the latter was much incensed by the question. Mr. Leavitt had no doubt that it was all one strand. Had it not been the hair would not have been sacred to Plenty Coups, and it seemed to be so beyond all question. There was some reddish ceremonial paint in the hair, which was itself black or dark brown. Through the interpreter it was learned that Leavitt and Scott were the only white men to whom it had ever been shown. The Indians considered the length to have been 99 hands (about 1,006 cm.) and that most of it had been given to Plenty Coups but some to others.

Comparison of this length with that reported by the travelers and traders presented a gap. Even the lesser dimension was freakish, while the greater one was almost incredible. If the average rate of growth of scalp hair is put at 6 inches (15.24 cm.) a year it would require fifty years to arrive at such length. There would probably be less growth in infancy and old age, illness might check it and privation (a not infrequent experience among Indians of that era) could interfere with the normal production.

Long ago Pincus<sup>5</sup> observed that the life of a single hair (except during childhood) was from two to six years and that when cut short it grew quickly for a time (2 to 5 mm. every ten days). According to him, when hair was of middle age, stood uncut for two years and was 10 to 14 inches (25 to 36 cm.) long, the rate of growth dropped to half that figure. He estimated the average length of hair when uncut as from 22 to 28 inches (55 to 70 cm.), with 36 inches (90 cm.) an exception. To attain such length, as frequently occurred among these Indians and especially in the chief in question, there could have been no loss and renewal to any extent and no slowing down in the rate of growth.

Persons who had the opportunity to measure the hair during life might have observed a greater dimension than was present in the strands cut after death, depending on the distance from the scalp that the hair was clipped. To preserve as much length as possible, the

4. One hand is equal to 4 inches (10 cm.).

5. Pincus, J.: Hair: Its Treatment in Health, Weakness and Disease, London, Chatto & Windus, 1882.

most interesting feature, it is presumed that the hair was cut close to the scalp. The fact that the hair was described as black or dark brown would seem to indicate, though not necessarily so, that the Indian was not extremely old at the time of his death. If so, the length was attained fairly early in life. Ten feet (305 cm.), at the rate mentioned, could have been reached between the twentieth and thirtieth years without undue acceleration, provided that there was no interruption of the natural life of the hair, as Pincus suggests. Twenty-five feet (762 cm.) seems excessive. Could the "red ceremonial paint" have been there for a purpose other than decorative and have served as an adhesive in or a camouflage of splicing? Might not Plenty Coups have been sincere in his veneration, but victimized by an earlier possessor? Was Max Bigman's count somehow increased to make an intentionally impressive figure? In the darkness of the ceremonial chamber some trickery might have been imposed on the "pale faces" as, for instance, overlapping of the hairs in echelon. Speaking of the Assiniboins' hair, Catlin<sup>6</sup> said:

I find the great length is produced by splicing or adding on several lengths, which are fastened very ingeniously by means of glue and the joints obscured by a sort of paste of red earth and glue, with which the hair is at intervals of every 2 or 3 inches [5 or 7.5 cm.] filled and divided into locks and slabs of an inch [2.5 cm.] or so in breadth.<sup>7</sup>

A last word came from Mr. Robert Yellowtail,<sup>8</sup> Superintendent of Crow Agency, Montana, speaking of Long Hair himself, ". . . his hair . . . was kept by Chief Plenty Coups. What happened to it when he died is not known." Apparently the last chance to investigate this particular strand has been lost forever.

#### COMMENT

While doubtless in books of travel and biography there exist accounts of races or persons with exaggerated growth of scalp hair, I have not encountered other possibly record-breaking instances. Hairy freaks reported in medical literature were mainly persons in whom hirsuties developed in situations in which normally only lanugo grew. Hubbard<sup>9</sup> wrote of a long-surviving California "forty-niner" with a beard over 7 feet (213 cm.) long, and that ". . . numerous instances are recorded where ladies' hair has attained a length of

6. Catlin,<sup>1</sup> p. 55.

7. Women's hair was cut as a form of punishment or when they were in mourning. The severed hair was sometimes used by splicing to increase the length of the hair of the braves in the tribes.

8. Yellowtail, R.: Personal communication to the author.

9. Hubbard, S. D.: A Treatise on Diseases of the Hair and Scalp, Philadelphia, Lea & Febiger, 1928, p. 50.

over 6 feet [183 cm.]." He gave no references to substantiate the last statement.

Savill<sup>10</sup> said that ". . . some writers have stated that they have seen hair 7 and 9 feet [213 and 274 cm.] long: there are frequent allusions to such cases in romantic poems and tales." I have been unable to trace any back to the original sources. Queues of the Chinese have not been mentioned as more than of floor length and were sometimes bolstered by the addition of extraneous fibers. Smith<sup>11</sup> said, "The . . . Chinese let theirs grow much longer than the Australian aboriginal men, whose hair is not long enough for a queue." No mention of East Indians with extraordinarily long hair was encountered. Danforth<sup>12</sup> and his associates did not recall instances of unusually long scalp hair. My personal recollection of the 7 Sutherland sisters, a group of women with magnificent hair reaching approximately to the floor who were exhibited to promote the sale of hair preparations, was that their tresses were somewhat over 5 feet (152 cm.) long in some instances.

We have, then, various opinions as to the actual length of the Indian's hair: General Hugh L. Scott and Scott Leavitt, 25 feet 5 inches (775 cm.), and Robert H. Lowie, summarizing the accounts of several early travelers, 9 feet 11 inches (302 cm.) to 10 feet 7 inches (323 cm.).

From the fact that this particular person stood out so prominently in this respect that even in a tribe of men excelling in growth of hair he was named Long Hair, it would seem that he had most unusual locks. Even the shortest length estimated constitutes a record in growth as far as I have been able to discover.

#### 136 South Sixteenth Street.

10. Savill, A.: *The Hair and Scalp*, Baltimore, Williams & Wilkins Company, 1945, p. 20.

11. Smith, R. B.: *The Aborigines of Victoria, etc.*, London, Trubner & Company, 1878, vol. 2, p. 243.

12. Danforth, C. H.: *Studies on Hair*, Arch. Dermat. & Syph. **11**:494 (April); 637 (May); 804 (June) 1925; **12**:76 (July); 195 (Aug.); 380 (Sept.); 528 (Oct.) 1925; personal communication to the author, 1945.

## ACIDITY OF THE SCALP

Nature and Possible Relation to Seborrhea

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**S**EBORRHEA and seborrheic skin are poorly understood terms that defy accurate definition. Nonetheless, experienced dermatologists develop some conception of them, though they may be embarrassed about putting it in writing. The one outstanding quality, oiliness, may indeed be absent in some cases, as in the dry varieties. Scaling, too, may be present or absent. Obvious inflammation may be lacking, or a severe degree of exudation can occur. Election of sites of large and numerous oil glands is a common denominator. The laboratory observations, too, are discouraging. Diverse organisms are seen. *Pityrosporum ovale*, observed often on the scalp, may be present in cases of seborrhea, but this observation is not constant. We are ignorant of what else may support the seborrheal state. The diathetic, the endocrine and the vegetative nervous factors, of course, have been considered in a theoretic way. It seems obvious that the problem must be surveyed more accurately and in detail. Among the biochemical angles which were thought worthy of investigation was the question of acidity of the scalp. The greater number of the normal subjects studied were medical students, mainly young men. The influence of washing the hair with soaps and other types of shampoo was studied. The extent of seborrhea was noted. Note was made as to the use of any tonics or other applications to the scalp.

Studies of the nature of the acids involved were made on scalp washings. The hair and scalp were rinsed thoroughly with a total of 200 cc. of distilled water. Lactic acid was determined by the method of Friedemann and Graeser.<sup>1</sup> Total volatile acids were determined by acidification with sulfuric acid and distillation with additions of water until all volatile acids had been driven over, followed by titration with

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1. Friedemann, T. E., and Graeser, J. B.: The Determination of Lactic Acid, *J. Biol. Chem.* **100**:291-308 (March) 1933.

phenolphthalein as an indicator, after the distillates had been aerated for fifteen minutes with air free from carbon dioxide.

### RESULTS

Analyses of scalp washings showed, in five tests made within twenty-four hours after washing of the scalp, average values for  $p_H$  of 5.7, for lactic acid 0.015 normal, for volatile acid 0.0011 normal, the volatile acid being 7 per cent of the total acidity. In seven tests made five to seven days after washing, the  $p_H$  was 5.2, the lactic acid 0.022 normal and the volatile acid 0.0051 normal, the volatile acid being 19 per cent of the total acidity. It is clear that the principal acid involved is lactic acid. A significant amount of volatile fatty acids was, however, also observed, amounting to from 4 to 33 per cent of the combined lactic and volatile fatty acid content. These results are similar to those obtained by us on sweat from other parts of the body and indicate that the acidity of the scalp is essentially the result of sweating at the surface of the scalp. It is interesting that a higher proportion of volatile fatty acids was noted on the scalp in tests made five to ten days after washing than in tests made when the scalp had been washed within twenty-four hours. This suggests that the volatile fatty acids are not secreted as such, but are at least largely formed on the scalp. Since our earlier studies on body sweat indicate that the volatile fatty acids are formed by bacterial action on lactic acid secreted in the sweat, it seems probable that a similar mechanism is involved here. Determinations of  $p_H$  were also carried out directly on the scalp, with glass or antimony electrodes. The 60 subjects used were mainly young men and women. Values varied from 4.3 to 6.1. The higher values were in general obtained in cases in which the hair had been washed within twenty-four hours and the lower ones in cases in which the hair had not been washed for several days. Thus, one day after washing values of 4.9 to 6.1 were obtained, with an average of 5.7. Two to four days after washing values of 4.9 to 6.0 were obtained, with an average of 5.4. After five to ten days values varied from 4.3 to 5.6, with an average of 5.1. The influence of washing was perhaps better shown by experiments made on 3 subjects at different times. These showed an average  $p_H$  the first day after washing of 5.6, after two days of 5.3, after five days of 5.2, after seven days of 4.8 and after ten days of 4.6.

The results indicate a decided effect of washing on the  $p_H$  of the scalp, showing that several days may be required for the acidity to be restored to a more or less stable value. That the reduction in acidity after washing was not due to alkalinity of the soap used was shown by the fact that washing of the scalp with shampoos not containing soap, such as K lauryl sulfates the solutions of which had an acid  $p_H$  of about 6.2, gave similar results.

That the acidity of the scalp may be responsible for a significant antibacterial action is indicated by the similarity of the acidity of the scalp to that of other surfaces of the body which have been more fully studied. We noted in previous studies<sup>2</sup> that the lactic acid of sweat might be expected to have a significant antibacterial action for a great variety of micro-organisms as long as the  $p_H$  was maintained at about 5.3 or below and that the volatile fatty acids might, because of their greater efficacy, extend the protection to about  $p_H$  6.2. While the exact concentration of acid at the surface of the scalp is difficult to estimate, it nevertheless seems clear that the  $p_H$  values of 4.5 to 5.5, commonly observed on the scalp, represent acidities having a definite antibacterial action, which may well be important in the prevention of infection of the scalp. We observed, for example, that growth of *Staphylococcus albus* and *Staphylococcus aureus* was inhibited at  $p_H$  5.4 by 0.025 normal volatile fatty acid and that *Streptococcus hemolyticus* was still more sensitive.<sup>3</sup> In fact, all the eighteen bacteria studied by us except *Bacillus acidophilus* were inhibited under these conditions and most of them by 0.01 normal acid at  $p_H$  5. The protection against yeast and other fungi which are less susceptible to the influence of acid might be expected to be less than for most bacteria, but still appreciable. The flora commonly observed on the normal scalp fits in with this view, few acid-susceptible organisms being commonly observed on the scalp. It is believed, therefore, that the acidity of the scalp may serve as an important protection against infections of various types. The antibacterial action of the scalp may be somewhat reduced for the first days after washing, but may still generally be adequate since some acid sweat may be secreted almost immediately.

That some relation may exist between acidity and itching of the scalp is indicated by the fact that itching of the scalp was often associated with low  $p_H$  values and was alleviated when the scalp was washed, with associated rise in  $p_H$ . Solutions of volatile fatty acids, such as acetic acid, with  $p_H$  values of 4.5 to 5 may produce some irritation when applied to the scalp of certain persons. The acids are also the only water-soluble irritant substances known to be present in scalp washings, with the possible exception of sodium chloride. That itching is not always present with high acidities indicates that it may be observed to vary with the irritability of the scalp, which may vary with different persons and with the condition of the scalp at the moment. Also, if the cutaneous

2. Bergeim, O., and Cornbleet, T.: The Antibacterial Action of the Lactic Acid and Volatile Fatty Acids of Sweat, Am. J. M. Sc. **205**:785-792 (June) 1943.

3. Bergeim, O.: Toxicity of Intestinal Volatile Fatty Acids for Yeast and Esch. Coli, J. Infect. Dis. **66**:222-234 (May-June) 1940. Bergeim, O.; Hanszen, A. H.; Pincussen, L., and Weiss, E.: Relation of Volatile Fatty Acids and Hydrogen Sulfide to the Intestinal Flora, J. Infect. Dis. **69**:155-166 (Sept.-Oct.) 1941.

## PERSISTENT LOCALIZED BULLOUS ERUPTION ASSOCIATED WITH FOCAL INFECTION

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WITHIN one year I have encountered 2 strikingly similar instances of a persistent localized bullous eruption of the skin in elderly patients that apparently was due to focal infection of the teeth.

### REPORT OF CASES

CASE 1.—Mr. W. M., a white man 70 years of age, was referred to me on Feb. 21, 1945 with a bullous eruption of his wrists of three months' duration.

*History.*—The patient was employed by the street department of his city. For about two years his work consisted of heating tar for roads. His wrists were always exposed to the steam from the boiling tar, and sometimes liquid tar actually splattered onto his hands and wrists. He used fuel oil to remove the tar from his skin. The patient did not have any cutaneous discomfort until the summer of 1944, when he noticed itching and an irritation of his wrists. This irritation did not clear up, even when he changed his work to shoveling snow in the winter. In December 1944 he noticed blisters on his wrists and around his ankles. This bullous eruption improved when he stopped working, but never healed completely. The patient thought that the blisters were caused by tar. He denied taking any drugs.

*Examination.*—Large bullae were noted around both wrists, some of them filled with pus. Healing blisters were present on both ankles. There were also crusted lesions on his back. The lesions caused only slight itching, but considerable "burning." There was no evidence of Nikolsky's phenomenon. Cultures from blisters both on plain agar and on crystal violet blood agar were negative several times. In two instances staphylococci and a few chain-forming gram-positive cocci were observed. The latter were identified as pneumococci in one instance. A smear from a blister showed 19 per cent eosinophils. The eosinophils in the blood varied from 2 to 3 per cent. Reactions to routine patch tests, including tests with coal tar, were negative. Bacterial tests elicited a severe tuberculin type of reaction to *Streptococcus hemolyticus*. At one time this antigen produced a central blister superimposed on the erythematous reaction, a rather unusual phenomenon. However, this phenomenon could not be duplicated. Reactions to intradermal tests with various staphylococcal antigens were negative.

The general examination revealed the teeth to be in a poor state. Roentgenograms of the teeth showed many root fragments and abscesses (fig. 2). Otherwise there were no noteworthy observations of disease.

*Course of the Disease.*—A tentative diagnosis of staphylococcal impetigo was made, and the usual treatment of this disease was prescribed. New blisters con-

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tinued to occur. Therefore, the patient was hospitalized on March 5, 1945. He was treated locally with silver nitrate, gentian violet medicinal and a rivanol zinc oil (2-ethoxy-6,9-diaminoacridinium hydrochloride 0.6 Gm., ichthammol 1.2 Gm., zinc oxide 24.0 Gm. and olive oil [or corn oil] to make 60.0 cc.); still new blisters appeared beneath the bandage. On account of the persistence of the lesions, the sterility of fresh blisters and the high eosinophilia of the vesicular fluid, the

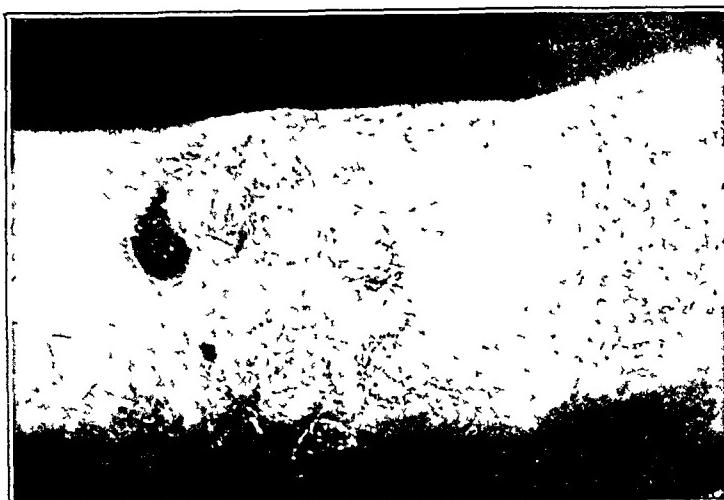


Fig. 1 (case 1).—Bullous eruption of the wrist resembling staphylococcal bullous impetigo, as it appeared when the patient was first seen.

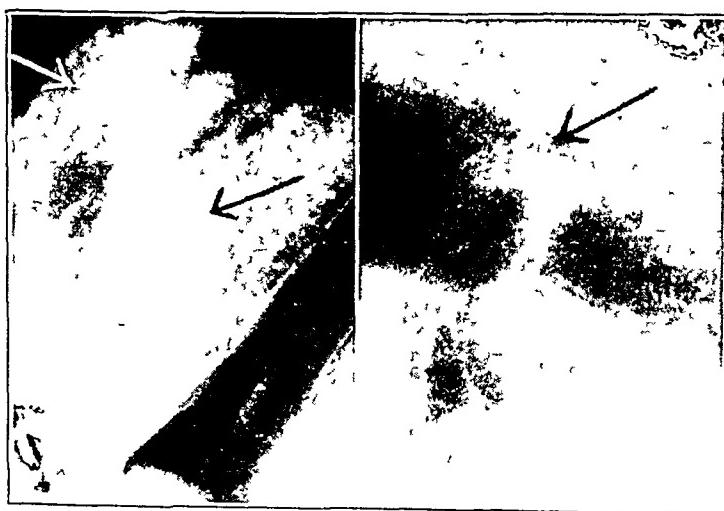


Fig. 2 (case 1).—Roentgenograms of abscessed teeth (enlarged). The abscesses can be seen as light areas around the roots (arrows).

possibility of dermatitis herpetiformis or pemphigus vulgaris was considered. Treatment with sulfapyridine did not produce any change. Treatment with sulfathiazole also was tried without success. There was slight improvement following treatment with penicillin, inasmuch as fewer new blisters appeared. At that time the possibility of a causative connection between the patient's eruption and his infected teeth was considered, and extraction of his teeth was recommended. The

patient hesitated one more month. During that time the bullous eruption continued. Then he had his remaining teeth removed. Within three to four weeks after the extraction of the teeth the blisters stopped recurring, and the patient has been well up to the time of writing (one year).

**CASE 2.**—A similar case was observed a year later. Mrs. M. G., 58 years of age, was referred to me on Jan. 7, 1946 because of a bullous dermatitis of the lower part of the left leg, of several months' duration.

**History.**—Four months before the patient had injured her left ankle. The site of this injury began to itch and swell, and a blister appeared. After this more bullae occurred, not only at the original site but also on the wrists and forearms. The patient felt well in general. She knew that she had a bad tooth, but the dentist had refused to extract it on account of her cutaneous disease. The patient did not take any drugs. Treatment by the family physician was unsuccessful. Therefore, he recommended hospitalization.

**Examination.**—At the time of the patient's admission to the hospital the left ankle was swollen and covered with numerous pea-sized to bean-sized blisters,



Fig. 3 (case 2).—Roentgenogram of teeth (enlarged), showing partial destruction and apical abscess of right lower bicuspid.

which extended upward along the lower part of the left leg. Redness and signs of healed blisters were noted on the wrists. There was no evidence of Nikolsky's phenomenon. The general examination revealed mild hypertension and moderately infected tonsils and teeth. The roentgenologic examination of the teeth revealed one right lower bicuspid to be partly destroyed with an apical abscess (fig. 3).

**Course of the Disease.**—A clinical diagnosis of bullous staphylococcal impetigo was made. Like the patient in case 1, this patient did not respond to the routine treatment for staphylococcal impetigo, although it was carried out at the hospital with utmost care. New blisters continued to occur even after the patient received penicillin, 20,000 units five times a day. However, there were fewer new bullae during the penicillin therapy. As a result of the observations in case 1, removal of the infected tooth was recommended. After the patient left the hospital more blisters appeared for a few more weeks until the infected tooth was removed. Shortly after the extraction her bullous eruption disappeared. The patient has been well up to the time of writing (three months).

## COMMENT

The observations in these 2 cases seem significant for two reasons. They demonstrate again the importance of focal infection for certain dermatologic diseases and help to explain the cause of certain benign bullous eruptions.

*Role of Focal Infection.*—The significance of focal infection for the pathogenesis of dermatologic diseases is still a matter of discussion.<sup>1</sup> In my opinion focal infection plays a much greater part than is generally recognized, especially in the pathogenesis of various forms of eczema. However, it is not within the scope of this report to deal in detail with focal infection in dermatologic diseases. In the 2 cases the relationship between the bullous eruption and the infection of the teeth seems definitely established. This claim is based on the following observations. 1. Focal infection in the form of abscessed teeth had been demonstrated. 2. All local and general treatment carried on for many months proved unsuccessful. 3. Removal of the focal infection led to a rapid and permanent cure of the eruption.

A few more observations that point further to the causative role of the focal infection might be added. Among them are the bacteriologic studies carried out in case 1. The blisters apparently were not due to a direct infection of the skin. The fluid from fresh blisters was sterile. The positive smears and cultures from the content of two older blisters can be interpreted as due to secondary invaders, as it is well known that any bulla may become contaminated in time. This viewpoint is supported by the fact that in both these instances two different kinds of cocci were observed.

Most phenomena in what is called focal infection actually are due to allergy rather than infection. In the 2 cases some observations point in the direction of an allergic reaction, among them the high eosinophil count of the blister fluid and the severe partially vesicular reaction elicited by the intradermal injection of a streptococcic vaccine.

These observations and facts taken together seem to fulfil the requirements for establishing an etiologic relationship between the bullous eruption and the focal infection. Another question remains: Why did the apparently long-standing and quiet focal infection suddenly produce the bullous eruption? The answer in these 2 cases may be based on the preceding trauma. The role of trauma in regard to the localization of manifestations of focal infection is known. In both cases trauma antedated the eruption. In case 1 the bullous eruption was preceded by chronic dermatitis. The occurrence of this dermatitis during the summer months, the history of close contact with tar and

1. Ormsby, O. S., and Montgomery, H.: Diseases of the Skin, ed. 6, Philadelphia, Lea & Febiger, 1943, p. 74.

the negative reaction to the patch test with tar make it appear likely that this was dermatitis from sensitization to sunlight caused by the tar. In the second case the patient definitely reported a mechanical injury as the eliciting factor. It is noteworthy that in both instances the bullous eruption occurred originally at the exact site of the preceding trauma.

*Differentiation from and Relationship to Other Bullous Eruptions.*—The bullous eruptions observed in cases 1 and 2 had to be distinguished mainly from bullous staphylococcal impetigo, dermatitis herpetiformis and pemphigus vulgaris. A bullous eruption due to drugs was excluded by the history and the observation during the hospitalization of the patients.

*Relationship to Bullous Staphylococcal Impetigo:* Clinically these cases resembled bullous staphylococcal impetigo, although the location of the eruption was atypical. Furthermore, staphylococcal impetigo usually occurs during the hot summer months.<sup>2</sup> Both cases originated in late fall.

The prolonged course, the sterility of fresh blisters, the continued appearance of bullae in spite of appropriate local therapy and especially the failure of sulfonamide drugs and penicillin ruled out bullous staphylococcal impetigo.

On the other hand, the ineffectiveness of the internal treatment with sulfonamide drugs and penicillin is quite compatible with the assumption of a focal infection. Much penetration of sulfonamide drugs or penicillin from the blood stream into the root abscesses cannot be expected.

Still there seems to exist a certain relationship between the eruptions described and bullous staphylococcal impetigo. It has been demonstrated that allergic phenomena play a role in the production of bullous lesions in staphylococcal impetigo.<sup>3</sup> In experimental infection with material from bullous staphylococcal impetigo, bullous lesions appeared on the seventh day at the site of the inoculations. In these experiments, the incubation period and the further course demonstrated a state of localized sensitivity to staphylococci. However, in staphylococcal impetigo there is a sensitivity to a local infection, whereas in the cases herein reported the sensitivity was due to a distant focus of infection.

*Relationship to Localized Bullous Dermatitis Herpetiformis:* Clinically, the eruption that has been described did not resemble the typical

2. Epstein, S.: Staphylococcal Impetigo Contagiosa, Arch. Dermat. & Syph. 42:840-855 (Nov.) 1940.

3. Epstein, S.: Local Allergic Phenomena in Circinatory Impetigo: Contribution to the Etiology of Staphylococcal Impetigo Contagiosa, J. Invest. Dermat. 3: 223-230 (June) 1940.

picture of dermatitis herpetiformis. Yet there are some factors which link these cases with dermatitis herpetiformis. There are cases of dermatitis herpetiformis that have been considered connected with focal infection.<sup>4</sup> Some authors<sup>5</sup> have expressed the belief that bacterial allergy plays a role in dermatitis herpetiformis. These investigators reported bullous reactions from intradermal injections of vaccines in their cases. In most instances these reactions occurred with *Escherichia coli*, but they have been also reported with *Staphylococcus aureus* and *Streptococcus hemolyticus*. I have seen in 2 instances of dermatitis herpetiformis bullous reactions from *Staph. aureus*. This reaction could be elicited repeatedly, though not always. Bacterial tests in hundreds of patients with dermatologic and other allergies as well as in controls have shown that bullous reactions are extremely rare with these antigens.

The case of Callaway and Sternberg<sup>5a</sup> is especially interesting because the patient exhibited numerous foci of infection in the lungs, teeth, tonsils and intestinal tract. In their case the removal of the teeth and tonsils produced severe flare-ups of the eruption. Desensitization with pneumococci cultured from the patient's bronchiectasis led to disappearance of the eruption, and overdoses of the vaccine apparently caused exacerbations. This case of Callaway and Sternberg is not comparable to the 2 cases of this report. But one may recognize a relationship between the atypical bullous eruption caused by a single focus of infection and the more complicated sensitization phenomena in Callaway and Sternberg's case that presented the typical picture of dermatitis herpetiformis.

I may mention, furthermore, reports of dermatitis-herpetiformis-like eruptions which apparently were bullous dermatophytids.<sup>6</sup>

The common denominator of these observations and the 2 cases of this report may be that of a bullous allergic reaction based on bacterial allergy.

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4. Riecke, E.: Dermatitis Herpetiformis, in Jadassohn, J.: Handbuch der Haut- und Geschlechtskrankheiten, Berlin, Julius Springer, 1931, vol. 7, pt. 2, p. 549 ff.

5. (a) Callaway, J., and Sternberg, T. H.: Bacterial Allergy: An Etiologic Factor in Dermatitis Herpetiformis, Arch. Dermat. & Syph. **43**:956-961 (June) 1941. (b) Swartz, J. H., and Lever, W. F.: Dermatitis Herpetiformis: Immunologic and Therapeutic Considerations, ibid. **47**:680-693, (May) 1943.

6. Tolmach, J. A., and Schweig, J.: Generalized Trichophyton Purpureum Infection Simulating Dermatitis Herpetiformis: Report of a Case Arch. Dermat. & Syph. **41**:732-735 (April) 1940. Peck, S. M., and Rosenfeld, H.: Recurrent Bullous Eruption (Duhring's Disease?) Treated with Trichophytin, ibid. **41**:812-813 (April) 1940.

There seems, however, a much closer link between my cases and some others in which observations were described as bullous dermatitis herpetiformis. In a report on 15 cases, Goodman<sup>7</sup> described a type that occurs mostly in elderly persons. It consists only of bullae, usually is localized and Nikolsky's phenomenon is not present. Apparently no search for a focal infection was made in Goodman's cases. There is a similarity between some of the observations in his cases and mine. It would seem to be appropriate to look for a focal infection in future observations of this type.

**Relationship to Pemphigus Vulgaris:** The cases of this report did not present the typical picture of pemphigus vulgaris. But the diagnosis of a localized pemphigus always has to be considered when a bullous eruption persists and no apparent cause, such as the use of a drug, can be established. There are reports in the literature about localized benign pemphigus, usually without Nikolsky's phenomenon. I can remember several instances of disease which were so diagnosed by others or by myself and which either cleared up or at least never turned into definite pemphigus. Goodman<sup>7</sup> stated the belief that they were of localized bullous dermatitis herpetiformis. Here, too, investigation in regard to focal infection seems indicated.

#### SUMMARY AND CONCLUSIONS

Two strikingly similar cases of a persistent localized bullous eruption of the skin in older persons are reported. They resisted anti-infectious external and internal treatment for many months, but cleared up rapidly and permanently after the removal of infected teeth. This eruption is considered to be due to focal infection. It is suggested that such a pathogenesis may be the basis for some of the cases described as localized bullous dermatitis herpetiformis or benign localized pemphigus.

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7. Goodman, M. H.: Bullous Dermatitis Herpetiformis, Arch. Dermat. & Syph. **46**:218-224 (Aug.) 1942.

STEP 1.—With a sharp scalpel or a razor blade the suspected lesion is pared down as much as possible. The diagnosis can then be confirmed by observing in the center of the callus the circumscribed verruca with several small dots in its center. These are the vascular papillae which are hypertrophied in a wart. A careful examination should also be made for satellite verrucae, which will be seen surrounding the central lesion and which are a frequent cause for failure of any method of therapy.

If vesicles or other signs of dermatophytosis are noted the treatment of the verruca must be delayed until the fungous infection is cured by other means. This is done to prevent an exacerbation of the dermatitis under the occlusive adhesive plaster.

STEP 2.—With a fine wooden applicator, a drop of 90 per cent phenol (so-called "liquefied crystals of phenol") is carefully applied to the top of the wart.

STEP 3.—With another wooden applicator, a drop of "fuming" concentrated nitric acid is applied directly over the phenol. A slight sputter is heard as the lesion turns dark brown. Practically no discomfort is experienced by the patient, although the sound may startle him at the first treatment.

STEP 4.—A rounded pad is devised with a piece of stiff felt or six to eight layers of adhesive tape. It should have tapering edges for comfort and a hole in the center which is the size of the verruca and which just fits over it. This is then applied to the foot. If multiple warts are present they can be treated by using separate pads or by having two holes in one pad.

STEP 5.—A small amount of ointment consisting of 60 per cent salicylic acid in petrolatum is placed in the ring. The ointment is used to soften the epidermis in order that it may be trimmed with ease at the time of the next treatment. The hole should not be completely filled with the ointment or it will prevent the adequate extrusion of the verruca. The entire pad, including the hole, is then covered and fastened to the foot with several strips of adhesive tape. These should be applied in such a manner that the pad cannot slip and the keratolytic ointment cannot escape.

After this treatment the patient is instructed to continue his usual activities. It is essential that the patient force the lesion into the well-like opening by walking on the pad. The use of the pad is an important part of the treatment, and it must be applied with care. To prevent it from slipping vigorous athletics, such as tennis, are prohibited. Bathing or showers are permitted, but the patient should be cautioned not to disturb the dressing.

In four or five days the dressing is removed, and the verruca with the surrounding callus is again pared down as thin as possible. At this time the skin will be observed to be white and soft from the action of the ointment. One should attempt to remove as much as possible of the dead epidermis without causing bleeding from the vascular papillae in the center of the wart. If bleeding occurs no harm is done, but several minutes should elapse to allow it to stop before the treatment is continued.

The same procedure, as previously outlined, beginning with the application of the phenol, is repeated and the lesion dressed in the same manner. Occasionally the verruca will become sensitive for the first

day or two after treatment. If this persists the treatment should be decreased by omitting the caustics or both the caustics and the ointment at the next treatment. The complete procedure can be resumed for the following treatment.

#### CRITERIA OF CURE

The number of times the lesion will have to be treated to obtain a cure depends largely on the age and depth of the verruca. At the completion of the treatment there must be a smooth continuity of the skin, with absence of the ring demarcating the wart from the surrounding skin, absence of the papillae in the center of the lesion and disappearance on palpation of the firm tender nodule of which the verruca is composed. The patient should be carefully examined at monthly intervals after the treatment has been completed to make certain that the lesion has not recurred.

#### RESULTS

The treatment described has been used on 100 patients treated under military conditions. In no instance has any serious reaction been observed. The number of applications used varied from two to twelve, the average being six. Of the 100 patients, 12 were assigned elsewhere before the period of treatment and observation could be completed. Of the 88 for whom treatment was completed and who were followed for at least one month thereafter, all but 1 were free of clinical evidence of a verruca when the course of therapy was completed.

The 1 patient for whom treatment was a failure had had repeated inadequate surgical excision and electrodesiccation over a four year period, with resultant scarring and distortion of the tissues. Of the 87 patients in whom the verrucae were obliterated by one course of treatment, 8 had a recurrence. Of these 8 patients it was possible to retreat only 5, because of military movements. But in all 5 a permanent cure was eventually obtained. It is felt that had it been possible to retreat the other 3 in whom there were recurrences, even a higher percentage of cures would have been effected.

#### SUMMARY

A specific and effective technic for the ambulatory treatment of plantar verrucae is described. It consists essentially of exposing the verruca with a ring pad and salicylic acid ointment and destroying it with phenol and nitric acid used successively. Although indiscriminate chemical cauterization of these lesions is not without danger, 100 consecutive patients were treated with the technic outlined with no untoward results. Eighty-four of the 88 patients (95 per cent), on whom follow-up examinations were possible, obtained a cure with this method.

A search of the available dermatologic and orthopedic literature did not reveal reference to this procedure.

## CHEMISTRY OF PALMAR SWEAT

### II. Chloride

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AND

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THE CHLORIDE content of general body or thermal-regulating sweat has been studied by many observers<sup>1</sup> under various conditions of increased temperature, humidity and work in both hot climates and thermal chambers. Values for chloride in the sweat, as previously reported, range from 52 to 700 mg. of sodium chloride in 100 cc. of sweat. The average, however, is about 250 mg. in 100 cc.

The studies on thermal-regulating sweat are important, because they contribute much to the knowledge of loss of chemicals and water from the body as a whole. However, they give only limited information on what the sweat gland itself can do. In other words, the study of profuse dilute general body sweat contributes to the knowledge of the skin in the same way that the study of renal function during profuse diuresis contributes to the knowledge of the kidney.

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From the Section on Dermatology and Syphilology (Dr. Lobitz) and the Department of Medicine, Abbott Laboratories, North Chicago, Ill. (Dr. Osterberg).

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(Footnote continued on next page)

Richards, Bordley and Walker,<sup>3</sup> and analyses for sodium chloride in the sweat were made by the capillary tube colorimetry method described by Westfall, Findley and Richards.<sup>4</sup> The estimations of sodium chloride in the urine and blood plasma were made by the method of Osterberg and Schmidt.<sup>5</sup>

Twenty normal subjects between the ages of 19 and 38 years were studied. Eleven subjects were women and 9 were men. Forty-seven successful collections and analyses were carried out (table).

As the personalities of different persons and the moods of each person vary, so does the output of palmar sweat vary in the same and in different persons. By observing the openings of the sweat ducts during the thirty minute collection of sweat we noted that the size of sweat droplets varied from gland to gland and stimulus to stimulus in the same and in different persons. Therefore the correlation of volume output and dissolved substances would yield varying information, and 2 persons could not be compared as to volume of sweat secreted. However, the manner in which the sweat was secreted could be consistently classified as one of three main physiologic types, and individual collections could be compared on this basis.

The three main physiologic types are as follows: Type I represents profuse sweating during the entire thirty minute period. The sweat gland never rested. This is the type of sweating encountered in thermal-regulating sweat, and it might be compared to diuresis in the kidney. Type III represents repeated secretion of moderate to small amounts of sweat, with periods when the sweat gland is at rest; in other words, the sweat came intermittently. Type II combines the features of type I and type III. There was profuse sweating during the first five to ten minutes and little intermittent sweating during the remaining period. In figure 1 the collections are represented graphically according to physiologic type.

In the earlier study twenty successful collections from 6 normal subjects (4 men and 2 women) were made. Of these collections four were type I, one was type II and fifteen were type III. By adding these twenty collections to the collections made in this study we have a total of sixty-seven successful collections of sweat for analysis of chloride (resulting from one hundred and seven attempts). Thirty-

3. Richards, A. N.; Bordley, J., III, and Walker, A. M.: Quantitative Studies of the Composition of Glomerular Urine: VII. Manipulative Technique of Capillary Tube Colorimetry, *J. Biol. Chem.* **101**:179-191 (June) 1933.

4. Westfall, B. B.; Findley, T., and Richards, A. N.: Quantitative Studies of the Composition of Glomerular Urine: XII. The Concentration of Chloride in Glomerular Urine of Frogs and Necturi, *J. Biol. Chem.* **107**:661-672 (Dec.) 1934.

5. Osterberg, A. E., and Schmidt, E. V.: The Estimation of Plasma Chlorides, *J. Lab. & Clin. Med.* **13**:172-175 (Oct.) 1927.

*Excretion of Chloride in Sweat of Normal Subjects*

Subject	Age, (Years), Sex	Physio- logic Type of Sweating	Volume of Sweat		Chloride		
			Collected from 50 Glands in 30 Min. in 0.35 Mm.* Tube, Mm.	Volume of Urine, Cc. per Min.			
			Mg. per 100 Cc.	Sodium Chloride			
J. M.....	21	III	1.00	3.60	1,000	322	600
	♀	III	0.35	0.38	780	1,263	607
		I	1.00	4.30	460	281	594
H. F.....	28	III	1.00	0.52	1,260	854	598
	♂	III	0.80	1.20	1,080	632	590
		III	1.30	1.30	1,020	1,310	587
E. G.....	28	III	0.80	0.48	880	854	621
	♀	II	3.70	0.40	680	1,521	590
		III	1.00	0.64	760	1,451	589
R. T.....	28	II	2.00	0.44	440	1,217	615
	♂	III	1.10	0.59	760	1,474	611
B. R.....	28	II	4.00	0.53	460	842	600
	♀	II	1.00	1.40	460	538	623
		II	1.50	1.80	460	304	598
M. B.....	19	III	0.60	0.025	780	1,100	615
	♀	II	0.60	0.44	300	1,544	615
		II	0.70	0.10	780	1,264	587
U. S.....	31	III	1.00	1.80	1,460	819	594
	♂	III	0.60	0.44	690	1,147	587
P. R.....	27	III	1.20	0.40	960	1,708	594
	♂	I	1.60	0.49	615	1,685	617
		III	0.50	0.30	1,200	1,451	598
J. L.....	27	III	0.40	1.20	1,520	1,310	598
	♂						
M. D.....	22	II	0.70	0.40	600	1,240	573
	♀	III	0.50	0.67	1,080	1,357	607
		III	0.30	1.41	1,000	257	581
E. L.....	28	I	2.20	0.37	320	1,381	598
	♀	III	1.00	0.24	760	913	598
M. M.....	20	II	0.80	1.70	330	866	598
	♂	II	0.55	0.82	630	1,661	623
		III	0.40	0.57	1,040	1,310	604
J. S.....	28	III	0.45	0.32	1,640	1,006	637
	♀						
H. H.....	28	III	0.50	0.47	1,500	1,217	611
	♀						
G. P.....	32	II	1.80	0.66	225	1,240	627
	♀	II	0.65	0.60	400	1,123	598
		II	0.30	0.50	650	1,123	611
R. T.....	33	III	0.40	0.64	1,040	1,708	600
	♀	III	0.40	0.80	1,480	679	598
A. P.....	22	II	6.00	1.40	215	819	594
	♀	II	0.70	1.00	300	1,264	598
		III	0.30	0.39	990	1,474	617
C. G.....	24	III	0.40	0.40	1,440	1,147	604
	♂						
P. M.....	33	III	0.30	0.30	1,040	1,720	617
	♂	III	0.45	0.51	1,560	1,451	600
L. R.....	28	III	0.40	0.60	1,220	1,638	611
	♂	III	0.80	1.02	1,095	1,310	627
		II	0.45	0.76	600	1,264	615

\* Inside diameter.

six of the collections of sweat were from women, and thirty-one were from men. The distribution as to physiologic type of sweating was as follows: type I, seven; type II, seventeen, and type III, forty-three.

In figure 2 the mean values and range of chloride secreted in the sweat in the sixty-seven analyses are represented graphically according to the three normal physiologic types. The values for chloride in urine and blood plasma for the same periods are also shown.

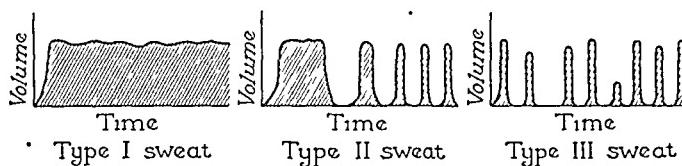


Fig. 1.—The manner of sweat output from an individual sweat gland; the so-called three physiologic types of sweating encountered.

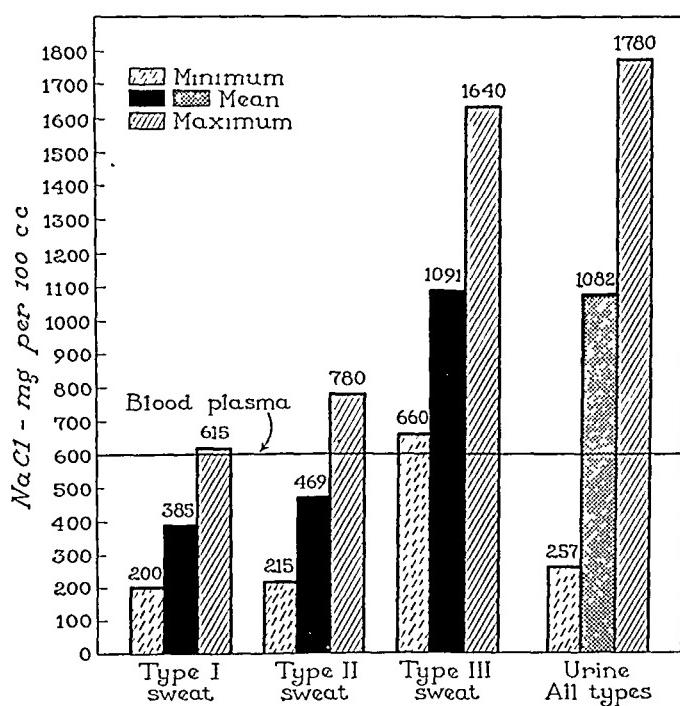


Fig. 2.—The mean values of chloride (expressed as sodium chloride) with minimum and maximum for the three physiologic types of sweating the urine in all types and the mean sodium chloride of the blood plasma in all types.

The mean value of 385 mg. of sodium chloride in 100 cc. (minimum 200 mg., maximum 615 mg.) in type I sweat agrees with the levels of sodium chloride reported in thermal-regulating or general body sweat, indicating that there are a sweat glomerulus and a tubule during the equivalent of diuresis.

A mean value for sodium chloride of 469 mg. per hundred cubic centimeters (minimum 215 mg., maximum 780 mg.) is observed in type II sweat. In this type the sweat gland may be regarded as a secreting unit partly in the equivalent of diuresis and partly not, but the greatest volume of output is during the so-called diuretic phase.

In type III the glomerulus and the tubule of the sweat gland work periodically and are shown to concentrate chloride as efficiently as the excreting units of the kidney. The mean value of sodium chloride is 1,091 mg. per hundred cubic centimeters (minimum 660 mg., maximum 1,640 mg.).

The values for chloride in the plasma were all within normal limits. The mean value of sodium chloride was 600 mg. per hundred cubic centimeters of plasma.

Readings of barometric pressures and of wet and dry bulb temperatures, in the laboratory as well as outside, during each collection showed these factors to have no correlation with the volume, physiologic type or concentration of chloride of the collected sweat.

#### SUMMARY AND CONCLUSIONS

By microscopic observation of duct openings of palmar sweat glands it is possible to classify the manner in which sweat is secreted into three main physiologic types: profuse, intermittent and a combination of profuse and intermittent.

The mean value of chloride (as sodium chloride) of sweat collected directly from duct openings of palmar sweat glands was 385 mg. per hundred cubic centimeters in profuse sweating, 469 mg. in the combined type of sweating and 1,091 mg. in the intermittent type of sweating. There was no correlation between these values and the content of sodium chloride in simultaneously collected blood (mean 600 mg. per hundred cubic centimeters) and urine (mean 1,082 mg. per hundred cubic centimeters).

The previously reported mean value of sodium chloride of about 250 mg. per hundred cubic centimeters of thermal-regulating, or general body, sweat agrees with the mean value of the profuse type of palmar sweat reported here.

The results of these studies give evidence that the palmar sweat gland can concentrate chloride to a greater degree than has been previously appreciated.

## STUDIES ON SENSITIVITY TO FORMALDEHYDE-TREATED STARCH

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THE NOXIOUS effect of talcum as used in surgeons' gloves has been stressed in the recent surgical literature.<sup>1</sup> This nonabsorbable powder causes a pronounced foreign body reaction in traumatized tissue and in the body cavities of both man and experimental animals (chest, abdomen, rectum, uterus, vagina). The commonest form of this reaction is chronic inflammation of the granulomatous type, progressing to the final stage of fibrosis, which when it occurs in the body cavities leads to the formation of more or less dense adhesions.

In view of these by-effects of talcum, a substitute powder has been recommended.<sup>1a</sup> This substitute is commercial corn starch, which as a result of treatment with formaldehyde has undergone a change in molecular structure. This change completely robs the starch of its gelatinizing properties, so that even when boiled or steamed in an autoclave it remains a free-flowing dusting powder.

The problem immediately calling for solution was the establishing of facts as to whether or not this material was comparatively innocuous, primarily irritating or capable of producing contact dermatitis after use on the skin. Patch tests were performed toward these ends.

The treated starch is prepared in the following way: Corn starch is subjected to formaldehyde vapor, under specific conditions of moisture, pressure and temperature. The free formaldehyde is then removed by washing or other suitable processes. This formaldehyde-treated starch produces no pathologic tissue response when applied to the skin or mucous membranes or injected into wounds or into the body cavities of experimental animals.<sup>1bc</sup> No pathologic tissue response is produced

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From the Dermatological Department of the Barnard Free Skin and Cancer Hospital and the School of Medicine, Washington University.

1. (a) Seelig, M. G.: Talcum as an Operating Room Hazard, South. M. J. **38**:470-472 (July) 1945. (b) Seelig, M. G.: Verda, D. J., and Kidd, F. H.: The Talcum Powder Problem in Surgery and Its Solution, J. A. M. A. **123**:950-954 (Dec. 11) 1943. (c) Seelig, M. G., and Verda, D. J.: The Talcum Powder Problem, J. Mt. Sinai Hosp. **12**:655-666 (May-June) 1945. (d) Seelig, M. G.: Abdominal Silicosis (Due to Talcum Powder) and Cancer, S. Clin. North America **24**:1162-1171 (Oct.) 1944.

when it is injected into the anterior chamber of the rabbit's eye.<sup>2</sup> It seems that it is almost immediately acted on by the normally present diastase of the body fluids, converted into a saccharide and absorbed.

The type of testing performed has been designated as the "prophetic patch test" technic by Dr. Louis Schwartz and Dr. Samuel Peck, of the United States Public Health Service,<sup>3</sup> and was recommended by them for use in foretelling whether or not a substance will produce dermatitis after contact with the skin. Two separate tests are made, ten to fourteen days apart, on the same person. Two hundred persons are used just as in other standard studies with patch tests. It is presumed that reactions will occur in the first series if the substance tested is a primary irritant, provided that the person under observation has never had previous contact with the substance. The reactions induced by the second series of tests indicate the number of persons in whom sensitivity has been induced by the first patch test.

#### PROCEDURE IN PATCH TESTS

Three materials were used for the patch tests: (1) the formaldehyde-treated starch before it had been autoclaved for use in the operating room, (2) talcum (Merk & Co., Inc.) and (3) plain corn starch ("argo"). The plain corn starch ("argo") and talcum served as controls for the formaldehyde-treated starch.

A group of 208 volunteers was tested. These volunteers were employees and patients at the Barnard Free Skin and Cancer Hospital and patients at the St. Louis City Hospital, the Jewish Hospital and the Barnes Hospital. No patient suffered from systemic disease; most of them were from wards for patients with fracture. No one with cutaneous disease was tested. The ages of the volunteers ranged from 14 to 70 years, the average age being 47.8 years. The sexes were fairly equally represented. There were 102 women and 106 men. Eight of the patients were Negroes.

*Technic.*—1. The talcum, the plain starch and the treated starch were moistened with water and applied to pieces of gauze  $\frac{1}{4}$  inch (0.64 cm.) square and covered with standard "elastopatch" (Duke Manufacturing Company). 2. Patches were placed on the skin of the scapular and infrascapular areas, on the back of the arms and on the anterior and internal surfaces of the thighs (the back of the arms was the usual location). 3. Patches were removed approximately forty-eight hours later and the areas observed. The areas were again observed in ninety-six and one hundred and ten hours after the removal

2. Seelig, M. G.: Personal communication to the author.

3. Schwartz, L., and Peck, S. M.: The Patch Test in Contact Dermatitis, Pub. Health Rep. 59:546-557 (April 28) 1944.

of the patches. 4. Ten days or more after the patches were removed, fresh ones were applied at the same sites and steps 2 and 3 were repeated.

#### RESULTS

There was one positive reaction in the patch tests among the 208 volunteers. This patient did not react to the material patches when the patches were applied for the first time, but after the removal of the second group of patches, a positive<sup>4</sup> reaction of 2 plus was observed at the area where the treated starch had been applied. One week later this patient had a patch test with 5 per cent formaldehyde and was observed to be sensitive (3 plus positive). An interesting but none the less somewhat confusing aspect of the test on this particular person is that although she was not sensitive to formaldehyde starch in the first patch test and was sensitive in the second to pure 5 per cent formaldehyde solution, she did not react positively to formaldehyde starch in a third patch test.

#### SUMMARY

Patch tests were performed with a formaldehyde-treated starch. Untreated starch and talcum were used as controls. The "prophetic patch test" technic was used. Two hundred and eight volunteers were tested. No positive reactions were observed after the removal of the first series of patches. One positive reaction to the formaldehyde-treated starch was observed after the removal of the second series of patches. The 1 volunteer who reacted to this starch was observed to be sensitive to formaldehyde on further testing, but did not react positively in a third patch test with formaldehyde starch.

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4. One plus was a reaction of erythema, 2 plus erythema and edema, 3 plus erythema, papules and a few vesicles and 4 plus erythema, edema, many vesicles and in some cases ulceration.

# EFFECTS OF ROENTGEN RAY IRRADIATION ON THE TESTES OF RABBITS

Possible Harmful Effects on Human Testes from Low Voltage  
Roentgen Ray Therapy

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AND

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THE POSSIBILITY of damaging effects to the body of patients caused by low voltage roentgen ray therapy administered for dermatologic conditions is a constant problem to dermatologists. Radiation directed to the scrotum and adjacent areas in 4 male patients was said to have caused sterility, and in 2 other male patients it was thought likely that sterility had been produced by treatment with roentgen rays.<sup>1</sup> Although the amount of roentgen ray therapy given the patients was not stated, it was presumed that the treatments were responsible for their sterility. Since information is available concerning the tolerated dose of roentgen ray irradiation for human ovaries<sup>2</sup> but seems to be lacking in regard to human testes, it is difficult to evaluate such a report. It is well known, however, that in animals the spermatogonia and the fully developed spermatozoa in the semen, seminal vesicles or testes are more resistant to roentgen irradiation than are the spermatocytes or spermatids.<sup>3</sup> It has been shown, also, that fertile spermatozoa may be

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1. Hughner, M.: Sterility and the X-Rays, J. A. M. A. **104**:1808-1809 (May 18) 1935.

2. (a) Westing, S. W.: The Importance of a New X-Ray Effect for Our Daily Diagnostic and Therapeutic X-Ray Work, New York State J. Med. **40**: 1139-1144 (Aug. 1) 1940. (b) Mayer, M. D.; Harris, W., and Wimpfheimer, S.: Therapeutic Abortion by Means of X-Ray, Am. J. Obst. & Gynec. **32**:945-957 (Dec.) 1936. (c) Harris, W.: Therapeutic Abortion Produced by the Roentgen Ray, Am. J. Roentgenol. **27**:415-419 (March) 1932. (d) Peck, W. S.; McGreer, J. T.; Dretzchwar, N. R., and Brown, W. E.: Castration of the Female by Irradiations, Radiology **34**:176-186 (Feb.) 1940.

(Footnotes continued on next page)

observed in the semen of animals for periods as long as six to twelve weeks after administration of known sterilizing doses of roentgen rays to the testes.<sup>4</sup>

With many of the dangers inherent in low voltage roentgen ray therapy obviated by the use of modern types of x-ray tubes and equipment,<sup>5</sup> we have attempted to determine whether or not the potential danger of accidental injury to the gonadal tissues of men actually exists. The intensity of roentgen rays in scattered irradiation in air to which gonads might be exposed during the course of low roentgen ray irradiation of the face has been measured. The effect of direct roentgen ray irradiation on the testes of rabbits and the effect of direct roentgen ray irradiation on human testes have been studied.

#### STUDIES ON THE INTENSITY OF SCATTERED IRRADIATION

An adult-sized plastic dummy was employed as a subject for the studies on scattered irradiation. The dummy was placed on a standard x-ray table with its long axis lying at an angle of 90 degrees to the beam of roentgen rays. A technic of irradiation was used that would ordinarily be employed in the treatment for acne vulgaris of the face. A Victoreen roentgen meter was then arranged to record the intensity of the scattered irradiation in the air at a distance of 75 cm. from the point at which the x-ray tube was focused (fig. 1). This distance was used because it represents the average distance from the face to the gonadal region in most men. A standard Westinghouse "dermadex" shock-proof x-ray machine with valve-tube rectification was used in generating the irradiation. The x-ray tube used was a standard Westinghouse x-ray tube with a half-value layer of 0.35 mm. of aluminum. The formula for irradiation was 85 kilovolts, 3 milliamperes, no filter and a tube distance of 10 inches (25.4 cm.). The x-ray machine was

3. (a) Oslund, R. M., and Bachem, A.: Geminal Epithelium in X-Rayed Testes of Rats, Proc. Soc. Exper. Biol. & Med. **23**:761 (April) 1926. (b) Warren, S. L.: The Physiologic Effects on Roentgen Radiation upon Normal Body Tissues, Physiol. Rev. **8**:92-129 (Jan.) 1928. (c) Snyder, L. H.: Roentgen Ray Induced Sterility and the Production of Genetic Modifications, Am. J. Roentgenol. **14**: 241-243 (Sept.) 1925. (d) Hooker, D. R.: The Effect of Exposure to Roentgen Rays on Reproduction in Male Rats, ibid. **14**:327-336 (Oct.) 1925. (e) Gatenby, J. B., and Wigoder, S. B.: The Effect of X-Radiation on the Spermatogenesis of the Guinea Pig, Proc. Roy. Soc., London, s. B **104**:351-370 (March) 1929. (f) Asdell, S. A., and Warren, S. L.: The Effect of High Voltage Roentgen Radiation (200 kv.) upon the Fertility and Motility of the Sperm of the Rabbit, Am. J. Roentgenol. **25**:81-84 (Jan.) 1931.

4. (a) Snell, G. D.: X-Ray Sterility in the Male House Mouse, J. Exper. Zoöl. **65**:421-441 (July 5) 1933. (b) Strandskov, H. H.: Effects of X-Ray on Inbred Strain of Guinea Pigs, ibid. **63**:175-202 (Aug. 5) 1932.

5. Taylor, L. S.: X-Ray Protection, J. A. M. A. **116**:136-140 (Jan. 11) 1941.

calibrated by a reputable physicist immediately before the studies were undertaken. Using the formula described, an output of 100 r per minute, measured in air, might be expected.

Repeated calculations with the Victoreen roentgen meter showed that with the conditions stated each 100 r directed to the face of the dummy resulted in an intensity of 0.034 r of scattered irradiation, measured in air, 75 cm. from the center of the roentgen ray beam. Since the average patient receiving roentgen ray therapy to the face receives not more than sixteen treatments of 100 r to each side of the face, a total of thirty-two exposures might be hypothesized. Assuming that the maximum of thirty-two exposures might be used in a given person, only 1.088 r ( $32 \times .034$  r) would be expected to reach the scrotal area during the entire series of thirty-two treatments.

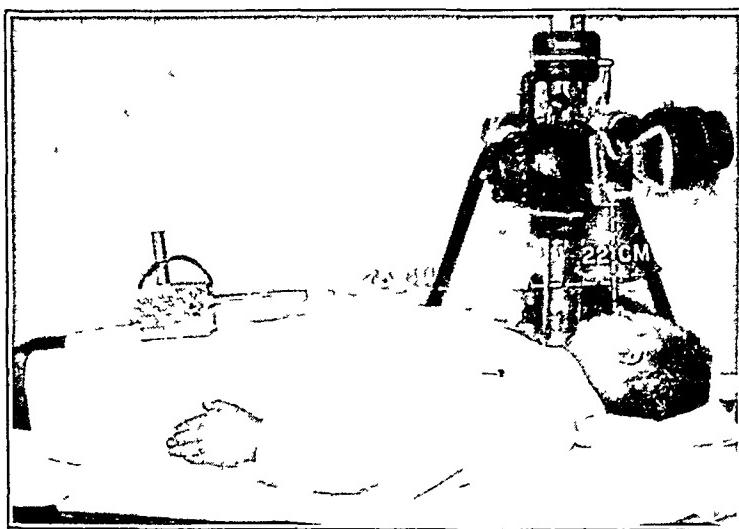


Fig. 1.—Technic used in measuring scattered irradiation.

#### STUDIES ON THE EFFECTS OF ROENTGEN RAYS ON RABBITS' TESTES

Our interest has been not only concerning how much roentgen ray therapy is required to sterilize animals completely but also concerning the amount required definitely to suppress spermatogenesis. We have undertaken to study the effects of varying amounts of roentgen rays in unfiltered low voltage roentgen ray therapy on the testes of rabbits. The number of spermatocytes, spermatids and spermatozoa in material aspirated from the testes was used as an index of the status of spermatogenesis. The technic employed consisted of irradiation of the testes with varying amounts of roentgen rays and, subsequently, studying microscopically material aspirated from the testes for evidence of the existing state of the spermatogenesis.

Five adult male white rabbits from the same litter were selected. Four of them were exposed to varying amounts of roentgen ray irradiation in gradually increasing doses (total dosage, 950 to 1,500 r).

When the animals were irradiated, they were placed on their backs in such a position that the roentgen ray beam would focus directly on the testes. The adjacent areas of the body were carefully screened with lead foil. The fifth rabbit was given no roentgen ray irradiation, but was examined at the same intervals as the irradiated rabbits and served as a control to eliminate the possibility of any harmful effect on spermatogenesis by the repeated aspiration of the testes. The control animal's spermatogenesis remained unchanged during the period of observation. The animals were kept in separate cages to prevent loss of spermatozoa through sexual acts.

At varying intervals an aspiration biopsy of the testes was made by inserting a 20 gage intravenous needle. A syringe containing 0.1 cc. of isotonic solution of sodium chloride was attached to the needle, and the solution was injected into the testicle, after which the plunger of the syringe was withdrawn by gentle traction. The needle was then withdrawn, and the material which had been aspirated was expelled on a warm glass slide, which was covered with a cover glass and rimmed with petrolatum, and examined under the high dry lens of a microscope. No staining methods were used. Sterile precautions were employed in the insertion of the needle into the testicle, and no infections were noted. The microscopic observations were recorded in terms of 1, 1 plus, 2 plus, 3 plus and 4 plus. Zero signified that no spermatocytes or spermatids or spermatozoa could be observed. One plus indicated only a few spermatids and motile or nonmotile spermatozoa; 2 plus indicated that spermatocytes, spermatids and spermatozoa were seen in at least every other microscopic field; 3 plus indicated spermatocytes and spermatids in every field and one to five motile spermatozoa, and 4 plus indicated that a normal number of germ cells were seen.

Observations were made at intervals over a period of eight months and were discontinued only after it was felt that a permanent arrest of spermatogenesis had occurred. Table 1 represents the observations on the entire group of animals, and the courses of the individual rabbits treated with roentgen rays are represented in graphs 1, 2, 3 and 4 in figure 2.

It can be seen that after 300 to 400 r of irradiation to the testicles deleterious suppressive effects on spermatogenesis could be recognized. However, at least 600 to 650 r are necessary before an arrest in spermatogenesis occurs. This arrest seems temporary. Nine hundred and fifty to 1,500 r are required to produce a permanent arrest in spermatogenesis.

Previous studies have shown that in mice 100 r to the testicles will induce a temporary suppression in spermatogenesis, but 800 to 1,600 r are necessary to induce sterility.<sup>4a</sup> Studies on guinea pigs have shown that from 422 to 864 r are required to produce temporary sterility.<sup>4b</sup> In rats at least 750 r are required to produce definitely recognizable depre-

TABLE 1.—*Details of Roentgen Ray Irradiation and Sperm Counts*

Day of Experiment	Rabbit 1			Rabbit 2			Rabbit 3			Rabbit 4			Control Rabbit	
	Dosage (r) Given	Total Dosage (r) to Date	Sperm Count	Dosage (r) Given	Total Dosage (r) to Date	Sperm Count	Dosage (r) Given	Total Dosage (r) to Date	Sperm Count	Dosage (r) Given	Total Dosage (r) to Date	Sperm Count	Sperm Count	
		Dosage (r) Given	Sperm Count											
1	200	200	4+	50	50	4+	-	100	100	4+	400	400	4+	4+
4	...	200	2+	...	50	4+	...	100	3+	...	400	2+	...	4+
11	...	200	3+	...	50	4+	...	100	3+	...	400	2+	...	...
28	200	400	...	200	200	...	200	300	...	200	600	...	...	4+
30	...	400	4+	...	250	4+	...	300	2+	...	600	0	...	...
33	150	550	...	200	450	...	200	500	...	...	600	...	...	...
35	...	550	2+	...	450	2+	...	500	2+	...	600	0	...	3+
37	50	600	...	50	500	...	50	550	...	...	600	0	...	...
39	...	600	4+	...	500	1+	...	550	1+	...	600	...	...	2+
42	75	675	...	75	575	...	75	625	...	...	600	...	...	...
44	...	675	1+	...	575	0	...	625	1+	...	600	...	...	4+
48	75	750	...	...	575	...	50	675	...	...	600	...	...	...
50	...	750	2+	...	575	1+	...	675	1+	...	600	0	...	2+
56	75	825	...	75	650	...	75	750	...	...	600	0	...	...
58	...	825	0	...	650	0	...	750	0	...	600	...	...	Bloody tap
64	...	825	0	...	650	0	...	750	0	...	600	0	...	...
122	75	900	3+	...	650	0	...	750	1+	...	600	0	...	4+
141	...	900	3+	...	650	0	75	825	...	...	600	2+	...	...
149	...	900	2+	...	650	1+	...	825	1+	...	600	2+	...	4+
157	300	1,200	...	300	950	...	300	1,125	...	300	900	...	...	4+
168	300	1,500	2+	...	950	0	...	1,125	0	...	900	2+	...	4+
187	...	1,500	0	...	950	0	...	1,125	0	300	1,200	0	...	...
215	...	1,500	0	...	950	0	...	1,125	0	...	1,200	0	...	4+
238	...	1,500	0	...	950	0	...	1,125	0	...	1,200	0	...	4+

sion of spermatogenesis.<sup>6</sup> Studies on the albino rat have shown that recovery from suppressed spermatogenesis is slow with 800 r and rare with 1,000 to 1,200 r, and when spontaneous regeneration occurs spermatozoa are rarely produced. Spontaneous regenerative changes are temporary, and involution follows fifty to eighty days after irradiation.<sup>7</sup>

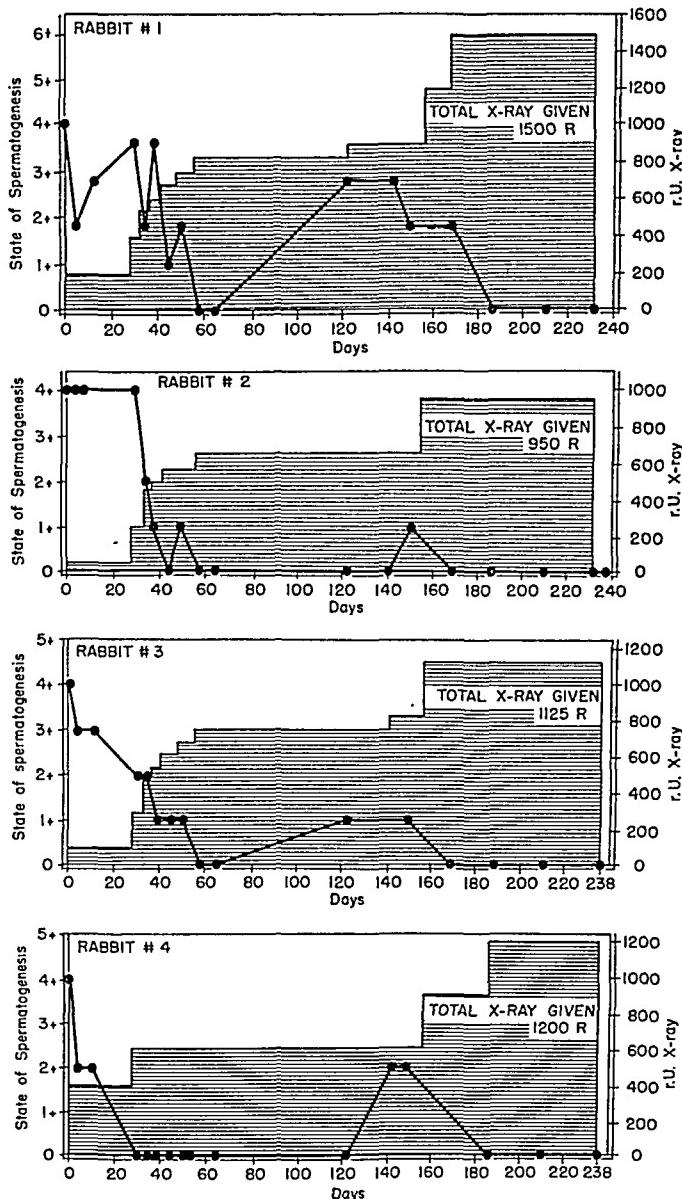


Fig. 2.—Detail diagrams of studies of roentgen ray irradiation and spermatogenesis.

6. Wigoder, S. B.: The Effect of X-Ray on the Testes, *Brit. J. Radiol.* **2**: 213-221 (May) 1929.

7. Momigliano, E., and Essenberg, J. M.: Regenerative Processes Induced by Gonadotrophic Hormones in Irradiated Testes of the Albino Rat, *Radiology* **42**: 273-282 (March) 1944.

It has further been reported that 12 per cent of rats given 800 r to the testes in one treatment show complete sterilization.<sup>8</sup> Gonads of sexually mature domestic fowl require 1,276 r for initial injury and 2,400 to 2,800 r for total destruction of seminiferous epithelium.<sup>9</sup> These observations are summarized in table 2, with observations in respect to effects of roentgen rays on the rabbits' testes.

#### BIOLOGIC STUDIES ON THE IRRADIATED ANIMALS

Five adult white male rabbits from the same litter were given respectively 300, 600, 900, 1,200 and 1,500 r to the testes, with the same irradiation factors as in the previous experiment. A sixth rabbit was used as a control. After three months' observation each of these rabbits was placed with a female rabbit to see whether pregnancy ensued. The control rabbit and the rabbits that received 300, 600 and 900 r respectively successfully impregnated a female, with a resulting litter of

TABLE 2.—*Amount of Roentgen Ray Therapy Necessary to Depress, Temporarily Arrest or Stop Spermatogenesis*

Animal Tested (Author)	Dosage (r) Necessary to Depress Spermatogenesis	Dosage (r) Necessary to Produce Temporary Arrest of Spermatogenesis	Dosage (r) Necessary to Produce Sterility
Rabbit (Callaway, Moseley and Barefoot)....	300 to 400	600 to 850	950 to 1,500
Mice (Snell <sup>4</sup> ) .....	.....	600	800 to 1,600
Rat (Wigoder <sup>6</sup> ) .....	.....	750	.....
Guinea pig (Strandskov <sup>4b</sup> ).....	.....	. 422 to 864	.....
Albino rats (Momigliano <sup>7</sup> ).....	.....	800	1,000 to 1,200
Domestic fowl (Essenberg and Karrasch <sup>9</sup> )....	1,276	.....	2,400 to 2,800

rabbits in each instance. The rabbits that had received 1,200 and 1,500 r respectively did not impregnate the female. Histologic study of the testes of these irradiated rabbits, killed after mating, showed that no arrest in spermatogenesis could be demonstrated on any of the testes of rabbits that received less than 1,200 r.

#### EFFECT OF IRRADIATION ON HUMAN TESTICLES

A 65 year old Negro man with carcinoma of the prostate gland was used for studies on irradiation. His scrotum was carefully shielded with lead, and 300 r was directed to the upper pole of the left testicle, 600 r to the lower pole of the right testicle, and 900 r to the upper pole of the right testicle. The lower pole of the left testicle was not irradiated

8. Hertwig, P.: Die Regeneration des Samenepithels der Maus nach Röntgenbestrahlung, unter besonderer Berücksichtigung der Spermatogonien, Arch. f. exper. Zellforsch. **22**:68-73, 1938.

9. Essenberg, J. M., and Karrasch, R. J.: An Experimental Study of the Effect of Roentgen Rays on the Gonads of the Sexually Mature Domestic Fowl, Radiology **39**:238-365 (March) 1940.

and was used as a control. In all instances the irradiation was filtered through 1 mm. of aluminum with a formula of 85 kilovolts and 5 milliamperes at a distance of 10 inches.

Three weeks later he was admitted to the hospital and a bilateral orchiectomy was performed. Both testes were obtained for histologic study, and sections were obtained from upper and lower poles of both testes.

In all of the microscopic sections there was atrophy of the seminiferous epithelium with no active spermatogenesis. There were, however, no discernible effects on the interstitial tissue from roentgen ray therapy in any of the sections.<sup>10</sup>

The second patient studied, a 51 year old Negro man with carcinoma of the prostate, was given roentgen ray therapy directly to the testes, with a formula of 85 kilovolts and 5 milliamperes with an aluminum filter of 1 mm. at 10 inches (25.4 cm.). The upper pole of the right testis was used as a control, and the lower pole of the right testis was given 300 r, with the rest of the testis carefully screened to prevent back scatter. The left testis was shielded in the same manner and with the same formula was given 600 r to the upper pole and 900 r to the lower pole. Four weeks later a bilateral orchiectomy was performed and the testes were studied histologically.

Careful histologic study revealed some generalized atrophy and scarring of the tubules thought to be due to senile changes. There were some cytoplasmic edema and minimal degenerative changes in certain of the seminiferous cells in the three poles that received irradiation. In these areas there was a lack of clarity in the nuclear structure. However, there was no suppression of spermatogenesis in any of the sections. The poles which received 300, 600 or 900 r showed as much active spermatogenesis as did the control area. There were no vascular changes in any of the sections.<sup>10</sup>

Admittedly, the first patient was a poor subject for such a study because of the lack of active spermatogenesis. It is suggested, however, that patients with carcinoma of the prostate gland who will require an orchiectomy are a source from which material may be obtained for evaluation of the effect of roentgen rays on the male gonads. We are now attempting to further this investigation with additional patients under study. When such patients exhibit active spermatogenesis and are studied in statistically significant numbers, one should be able to settle the problem of the effect of roentgen rays on human testes.

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10. The histologic sections were studied in conjunction with Dr. E. C. Hamblen, Dr. Clarence Davis, and Dr. C. J. Pattee of the Division of Endocrinology and Dr. Cyrus Erickson, Dr. Thomas Lide, Dr. Lalla Iverson and Dr. J. T. Cuttino of the Division of Pathology.

## MYCOSIS FUNGOIDES

Benign and Malignant Reticulum Cell Dysplasia

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MYCOSIS fungoides has always been a subject for debate. Many investigators consider it neither a clinical nor a histologic entity. Therefore, they have placed it in the inclusive group of lymphoblastomas. Further support for this is the fact that mycosis fungoides may simulate other diseases of this group.

The histologic structure in the clinical picture of mycosis fungoides may be granulomatous, reticuloendotheliomatous or reticulosarcomatous. The reticulum of the skin is considered by many to be the site of origin. Some have thought that the perithelium, endothelium, adventitial or periadventitial histiocytes of the blood vessels in the cutis or the fixed connective tissue cells and fibroblasts were the matrix. The widespread character of the reticulum accounts for the generalized reaction, which is a constant feature of the disease.

The variable histologic appearance of mycosis fungoides is based on the many potentialities of differentiation of the reticulum cell. Scott and Robb-Smith,<sup>1</sup> on the basis of lymph node studies in reticulum cell sarcoma, classified five types of malignant reticulum cells: undifferentiated, differentiated to histioid cells, differentiated to hemic cells, mixed or polymorphic cells and differentiated to sinus lining cells. Furth<sup>2</sup> stated that most human neoplasms consisting of histiocytes were described under the term reticulum sarcoma. In mycosis fungoides the reticulum cells can form histiocytes, plasmacytes, fibroblasts and neoplastic reticulum or sarcoma cells. It is a transformation of one cell type into another rather than a neoplastic invasion. For this reason several investigators have considered mycosis fungoides as a step in dedifferentiation in the return of dermal tissue to an embryonal state.

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Read at the Sixty-Sixth Annual Meeting of the American Dermatological Association, Inc., Hot Springs, Va., June 10, 1946.

From the Division of Dermatology, University of Minnesota, and the Division of Dermatology, Minneapolis General Hospital.

1. Scott, R. B., and Robb-Smith, A. H. T.: Histiocytic Medullary Reticulo-Endotheliosis, *Lancet* **2**:194-198, 1939.

2. Furth, J.: A Neoplasm of Monocytes of Mice and Its Relation to Similar Neoplasms of Man, *J. Exper. Med.* **69**:13-29, 1939.

Mycosis fungoides has two definite histologic divisions, one in the premycotic stage and the other in the tumor stage. The histologic study of the premycotic stage shows slight epidermal changes of liquefaction necroses of the basal cells and intraepidermal microabscesses of Pautrier, consisting of nests of monocytes. In the cutis are the constant diagnostic polymorphous cellular conglomerations, consisting of lymphocytes, polymorphonuclear neutrophils, eosinophils, plasma cells, connective tissue cells, phagocytic histiocytes, nests of reticuloendothelial cells, pyknotic nuclei and fragmenting nuclei. The latter nuclear changes are due to the intense liquefaction necrosis, which gives a washed-out appearance to the cytoplasm of the proliferating cutis cells and is a characteristic of this stage of mycosis fungoides. In this phase, Gans,<sup>3</sup> Ormsby and Montgomery<sup>4</sup> and McCafferty and Machachek<sup>5</sup> stressed the pyknotic nuclei, karyorrhexis and phagocytosis of pigmented granular elements of debris. Jaffee<sup>6</sup> emphasized the richness of the eosinophilic leukocytes in this phase. Zoon<sup>7</sup> stated that the polymorphous image is so typical that it is impossible not to recognize the disease. Hematologists would classify this stage of mycosis fungoides as a complex reticulum cell proliferation, because of its polycellular nature.

In the tumor stage the histologic structure assumes a simple monomorphous pattern, with the cells in the cutis appearing more uniform. Nests of mitotic reticulum cells are evident. The cells appear to be joined by the reticulum fibers. In this stage the picture is that of a reticulum cell sarcoma. The characteristic reticulum cell, called the "mycotic cell," is most easily seen in this stage, being characterized by delicate cytoplasm and a large, round or oval nucleus. This cell is vulnerable and fades as though washed away.

This great vulnerability of the cells explains the clinical phenomenon of rapid spontaneous regression of the lesions of mycosis fungoides. Lapiere<sup>8</sup> and Margarot, Rimbaud and Ravoire<sup>9</sup> stated the belief that

3. Gans, L.: *Histologie der Hautkrankheiten*, Berlin, Julius Springer, 1925, vol. 1, pp. 565-575.

4. Ormsby, O. S., and Montgomery, H.: *Diseases of the Skin*, ed. 6, Philadelphia, Lea & Febiger, 1943, p. 818.

5. McCafferty, L. K., and Machachek, G. H.: *Lymphoblastoma: A Report of Two Cases*, Arch. Dermat. & Syph. **21**:595-614 (April) 1930.

6. Jaffee, R. H., in Downey, H.: *Handbook of Hematology*, New York, Paul B. Hoeber, Inc., 1939, vol. 2, pp. 1105-1107.

7. Zoon, J. J.: *Notes diagnostiques et therapeutiques au sujet du mycosis fongoïde*, Bull. Soc. fran<sup>c</sup>. de dermat. et syph. (Reunion dermat., Strasbourg) **44**:1282-1290, 1937.

8. Lapiere, S.: *Étude comparative du mycosis fongoïde et de la maladie de Hodgkin*, Rev. belge sci. m<sup>ed</sup>. **10**:159-171, 1938.

9. Margarot, J.; Rimbaud, P., and Ravoire, J.: *Quelques aspects cliniques et histo-pathologiques des hématodermies à forme tumorale*, Montpellier m<sup>ed</sup>. **15**: 211-228, 1939.

these cells originate from the histiocytes of perivascular tissue. In these cells the cytoplasm becomes enlarged and more granular, while the chromatin in the nucleus becomes irregular. Thus one can reconcile the frequent observation of phagocytic cells together with plasma cells, the latter of which are considered maturer forms of the histiocytes. The presence of reticulum mitotic figures indicates another of the multiphasic possibilities of reticulum proliferation. This characteristic has caused confusion and has resulted in the gross grouping of lymphoblastoma rather than in the classification of the several types of reticulum proliferation. Therefore, Fraser<sup>10</sup> and Wile and Styles<sup>11</sup> considered a mutation of clinical mycosis fungoides responsible for the cases which were observed at autopsy to be lymphosarcoma. Pardee and Zeit<sup>12</sup> reported a case in which mycosis fungoides became lymphatic leukemia just before death. Symmers<sup>13</sup> also reported a case of leukosarcoma in which a leukemic blood picture developed three weeks before death. Fraser's<sup>14</sup> case of premycotic fungoides was similar and two years later became "lymphatic leukemia." Montgomery and Watkins<sup>15</sup> reported cases of patients who clinically had lesions of mycosis fungoides, but the disease terminated in monocytic leukemia. Robb-Smith<sup>16</sup> stated that changes in the circulating blood are epiphomena in reticuloses. Although several have expressed the belief that there was a transition of mycosis fungoides to Hodgkin's disease and to lymphosarcoma and have described it, there is no definite method of predicting this mutation.

#### REPORT OF CASES

CASE 1.—B. P., a white woman aged 55, was admitted to Minneapolis General Hospital March 19, 1940, complaining of a large ulcer of the left leg of fifteen months' duration. The ulcer was 14.5 by 9.5 cm. and extended into the muscles of the calf to a depth of 2.5 cm. The base exuded a sanguinopurulent discharge which had a foul odor. From several specimens for biopsy only a chronic suppurative inflammatory reaction was indicated. The ulcer was thought to be due to old deep thrombophlebitis, since there was a history of phlebitis following parturition thirty-two years previously.

10. Fraser, J. F.: Mycosis Fungoides, *J. Cutan. Dis.* **35**:793, 1917.

11. Wile, U. J., and Styles, F., Jr.: Clinical Mutations in Lymphoblastomas, *J. A. M. A.* **104**:532-537 (Feb. 16) 1935.

12. Pardee, L. C., and Zeit, F. R.: Mycosis Fungoides, *J. Cutan. Dis.* **29**:7-19, 1911.

13. Symmers, D.: The Association of Certain Cutaneous Lesions with Diseases of the Hemopoietic System, *J. Cutan. Dis.* **37**:1-15, 1919.

14. Fraser, J. F.: Mycosis Fungoides: Its Relation to Leukemia and Lymphosarcoma, *Arch. Dermat. & Syph.* **12**:814-828 (Dec.) 1925.

15. Montgomery, H., and Watkins, C. H.: Exfoliative Dermatitis as a Manifestation of Monocytic Leukemia (Schilling), *Minnesota Med.* **21**:636-641, 1938.

16. Robb-Smith, A. H. T.: The Reticular Tissue and the Skin, *Brit. J. Dermat.* **56**:151-177, 1944.

An autopsy was performed, and the pathologic diagnosis was mycosis fungoides, with involvement of the skin, right lung, kidney and liver, and bronchopneumonia and pleural effusion of the right lung.

*Comment.*—The histologic section of the skin from the earliest ulcers showed a granulomatous process which consisted essentially of reticulum cells, histiocytes, plasma cells and fibroblastic proliferation. In some sections plasma cell nests were dense. Reticulum cells can proliferate to form plasma cells.

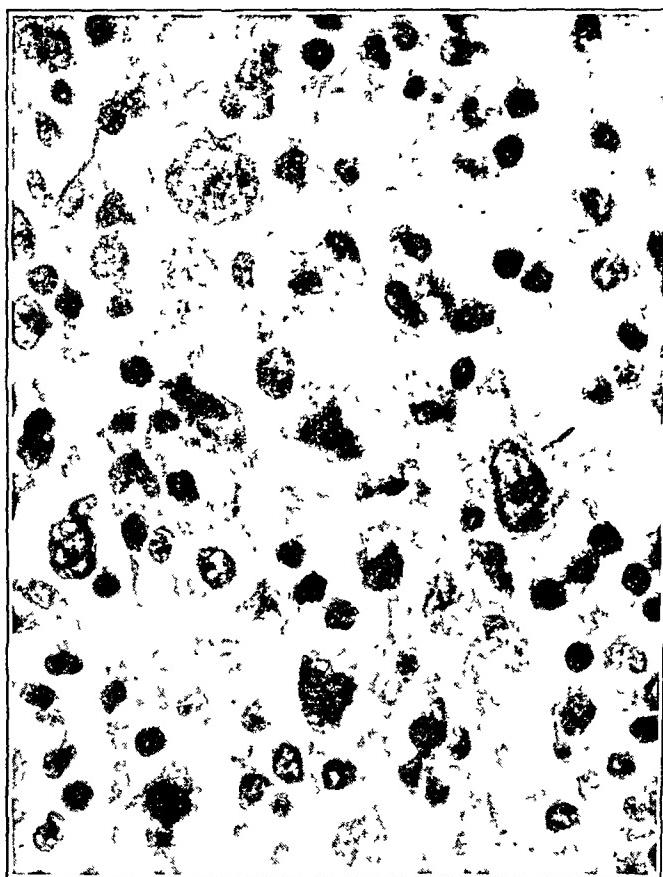


Fig. 2 (case 1).—Section of ulcer of figure 1, showing large histiocytes, plasma cells, lymphocytes and cell nests undergoing liquefaction necrosis.  $\times 650$ .

This case was mycosis fungoides of the *d'embrée* type. The lymph nodes were not involved. The lesion of the lung was confusing, as it was first diagnosed as primary pneumonia. At autopsy the gross pulmonary tumor looked like a bronchiogenic carcinoma. Only on histologic section could the diagnosis of mycosis fungoides be made. Berman<sup>17</sup> collected 60 cases of mycosis fungoides in which there was visceral

17. Berman, L.: Pathologic Nature of Mycosis Fungoides with Report of a Case, Arch. Path. 29:530-540 (April) 1940.

Observations of physical abnormalities were limited to the skin, which showed patchy areas of pinkish red circinate weeping lesions over the sacrum. An area 2 by 2 cm. and elevated 0.5 cm. was noted over the left lower quadrant of the abdomen. Many scaly indurated lesions were scattered over the body. There were numerous excoriations.

Histologic section of the skin from both the indurated areas of the abdomen and the eczematous areas over the sacrum showed pleomorphic cell nests of reticulum cells, lymphocytes, plasm cells, histiocytes and fibroblasts. Pyknosis and karyorrhexis were evident in the midst of the proliferating cells. The histologic diagnosis corroborated the clinical diagnosis of mycosis fungoides.



Fig. 4 (case 2).—Ulcerated tumor stage and horseshoe plaques of mycosis fungoides.

The patient was given roentgen therapy, 13 r of general radiation in each of eight treatments, to the front and back at 130 cm. distance, filtered with 0.25 mm. of copper and 1 mm. of aluminum at 130 peak kilovoltage and 5 milliamperes. After the eighth treatment the roentgen therapy had to be discontinued because of the pronounced reduction in the white blood cell count. He was discharged on November 4, but was readmitted March 28, 1944 because a tumor 10 by 15 cm. had developed over the sacrum. The inguinal lymph nodes were also noticeably enlarged. Biopsy specimens of skin, tumor and lymph nodes were taken. Histologically, the lymph node showed loss of normal architecture. The lymph follicles were replaced by reticulum cells, many showing various stages of mitosis. The

cutaneous sections showed replacement of the normal cutis by reticulum cell hyperplasia, and numerous mitotic figures were evident. The histologic structure had a striking monomorphic character, and the diagnosis of mycosis fungoides progressing to a reticulum cell sarcoma was made. The peripheral blood and bone marrow were normal. Roentgenograms of the stomach, lungs and heart showed nothing abnormal. The sacral tumor softened and ulcerated. The patient died on May 30. Permission for an autopsy could not be obtained.

*Comment.*—Clinically this patient had typical mycosis fungoides, in which severe itching preceded objective signs by six months and progressed from erythematous plaques (premycotic) to eczematous

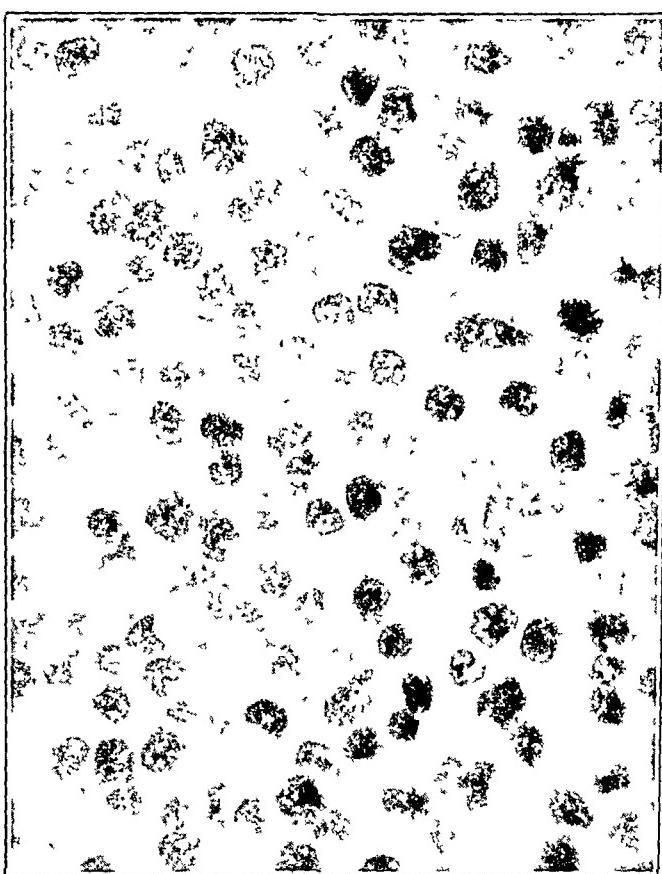


Fig 7.—Four mitotic figures.  $\times 650$ .

(mycotic) lesions, with indurated tumors, and finally to ulceration. Histologically, the early pleomorphic cellular infiltration and the late monomorphic cell proliferation were typical of mycosis fungoides. The reticulum cell sarcoma involved both skin and lymph nodes in this patient. Lymph node imprints were obtained and showed actively proliferating reticulum cells.

CASE 3.—E. A., a white woman aged 61 years, was admitted to the Minneapolis General Hospital Oct. 2, 1943, complaining of severe burning and itching of the skin, of one year's duration. At onset the eruption appeared as generalized

scattered large red macules which subsequently developed scales, then oozed and formed crusts. These crusted areas broke down and formed large painful chronic ulcers.

Physical examination revealed nothing unusual except for the skin, which was covered by numerous scaly and crusted plaques and ulcers. The eruption of the scalp was covered by grayish white firmly adherent scales and resulted in diffuse alopecia. There was pitting edema of the ankles.

Reactions to serologic tests of the blood were negative for syphilis. The hemoglobin was 54 per cent, the red cell count 2,770,000 and white cell count 7,600, with 66 per cent neutrophils, 14 per cent lymphocytes, 19 per cent monocytes and 1 per cent eosinophils. The platelet count was 310,000. The morphologic

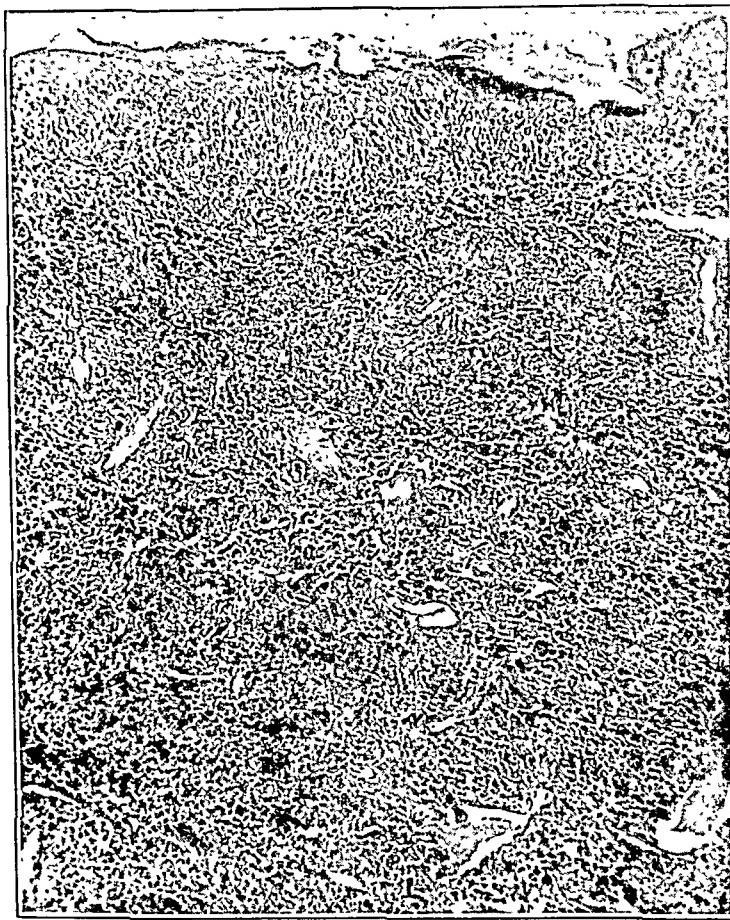


Fig. 8.—Photomicrograph of lesion of mycosis fungoides.  $\times 100$ .

study of the blood showed an average mean red cell diameter of 7.7 microns, with slight polychromasia, slight poikilocytosis and slight anisocytosis. Many of the red cells showed lipid degeneration. The white cells appeared toxic. Some of the monocytic cells appeared to be monocyteoid histiocytes. Examination of the urine revealed no abnormalities except for a faint trace of albumin. A roentgenogram of the chest showed thickening of the pleura of the wall of the right side of the chest.

Biopsy specimens of the ulcers and indurated areas of the skin were taken. Microscopic examination revealed that the cutis contained a pleomorphous cell infiltration, consisting of reticulum cells, fibroblasts, plasma cells, histiocytes and lymphocytes. Karyorrhexis was evident throughout the sections, as were numerous

phagocytic histiocytes. The histologic diagnosis of mycosis fungoides confirmed the clinical impression.

Roentgen rays were administered to the involved areas of the skin, and multiple small blood transfusions (200 to 300 cc. of citrated whole blood) were necessary to maintain the level of the hemoglobin. The skin improved appreciably for about six weeks, then there was general and gradual deterioration, and she died Feb. 27, 1944.

An autopsy was performed. Microscopic examination of a mesenteric lymph node showed reticular hyperplasia, but normal architecture. The spleen also showed reticular hyperplasia and an increase in the number of neutrophils and plasma cells. Some of the malpighian corpuscles were practically obliterated. The diagnosis was mycosis fungoides.

*Comment.*—The foregoing is a classic picture of mycosis fungoides, clinically and histologically. At autopsy the amount of gross pathologic changes present seemed insufficient to explain the severe toxic state of the patient. This can be accounted for by the tendency of mycosis fungoides to resolve itself and melt away. This phenomenon is also seen in the cases of mycosis fungoides which assume neoplastic characteristics, with involvement of regional glands and internal organs, and in which there is replacement of normal structures by neoplastic ones containing numerous mitotic figures. Cutaneous imprints and lymph node imprints were unsatisfactory, as they were made at autopsy and the cells had already undergone postmortem degeneration.

CASE 4.—A. W., a white woman<sup>19</sup> aged 76, was admitted to the hospital on Aug. 14, 1945, complaining of an eruption, which began two years previously as generalized itching erythema and exfoliation. The erythema and exfoliation subsided after about one year and were followed by indurated plaques and tumors, some of which ulcerated and then later healed leaving hyperpigmented rings in the skin.

Examination revealed the skin of the trunk, face and extremities to be involved by numerous indurated dusky red plaques and tumors, some of which were ulcerated. The dorsa of the feet and the anterior surfaces of the legs and thighs had dark bluish red firm nonelevated nodules, which were not ulcerated and which the patient stated came on six weeks before admission. The latter lesions did not itch. There was pitting edema of the legs and ankles. The clinical diagnosis was mycosis fungoides and idiopathic hemorrhagic sarcoma of Kaposi.

A specimen was taken for biopsy from an ulcerating tumor on the right shoulder. Microscopic section of this tissue showed nests of actively proliferating large reticulum cells and phagocytic reticulum cells or histiocytes and a few plasma cells. Tissue imprints showed large mononuclear reticulum cells with oval nucleus and finely granular vacuolated cytoplasm. The nucleus consisted of lacy chromatin and contained three large nucleoli. The diagnosis from the section was mycosis fungoides.

A biopsy was made from one of the firm nodular lesions on the lower extremities. Microscopic sections of this lesion showed that the cutis contained great nests of proliferating fibroblasts, new blood vessel formations and large amounts of extravasated blood. Tissue imprints from this nodule showed only fibroblasts.

19. Permission to present this case was granted by Dr. S. Ayres Jr.

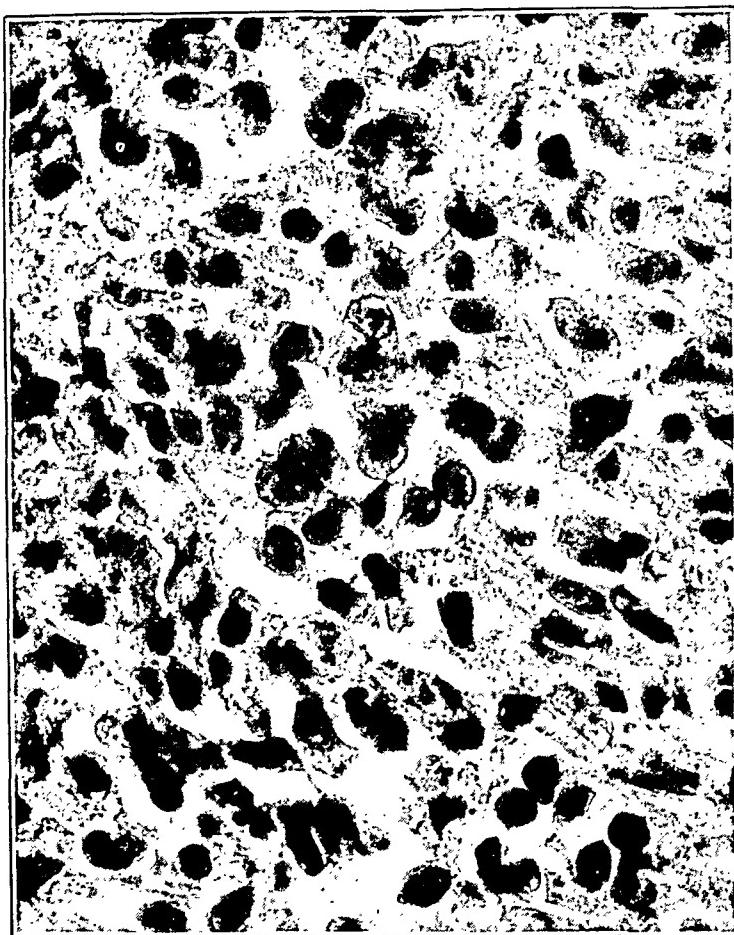


Fig. 9 (case 4).—Photomicrograph showing the phagocytic characteristics of the histiocytes.  $\times 650$ .



Fig. 10 (case 4).—Photomicrograph of malignant reticulum cell from a cutaneous tumor imprint of mycosis fungoides.  $\times 2100$ .

The histologic diagnosis of this nodule was idiopathic hemorrhagic sarcoma of Kaposi.

The patient was treated intensively with roentgen rays, subcutaneous and intravenous injections of antireticular cytotoxic serum (A. C. S.), repeated transfusions and intravenous injections of serum, all without altering the course of the disease, and she died Jan. 15, 1946. Permission for an autopsy was not granted.

It was observed in the final periods of the patient's illness that the cutaneous lesions began to regress and the skin looked closer to normal, but the patient's general condition became worse.

*Comment.*—From this case it is seen that both mycosis fungoides and idiopathic hemorrhagic sarcoma of Kaposi can exist in the same

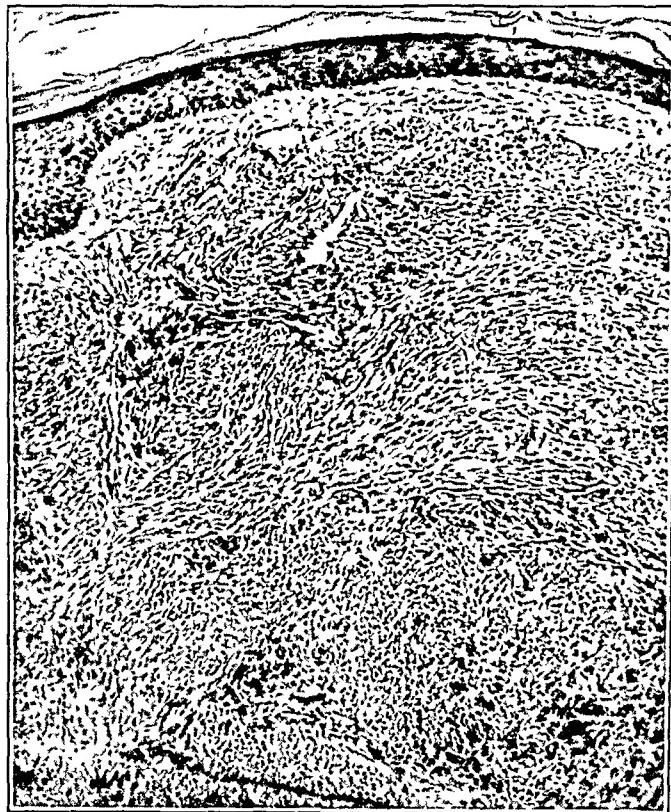


Fig. 11.—Photomicrograph of a lesion of idiopathic hemorrhagic sarcoma of Kaposi in case 4, showing intense fibrosis.  $\times 100$ .

patient, but their clinical course as well as histologic appearance differs and the types of cells seen on tissue imprints were not the same.

#### DIFFERENTIAL DIAGNOSIS

In the differential diagnosis Hodgkin's disease must be considered. Clinically Hodgkin's disease begins in the lymph nodes and secondarily involves the skin, with the exception of the rarely occurring primary Hodgkin disease of the skin. Mycosis fungoides, on the other hand, involves the skin first and the lymph nodes secondarily. Histologically,

in the tumor stage of Hodgkin's disease polymorphous cell structures are seen, whereas in the comparable tumor stage of mycosis fungoides cellular masses are monomorphous. Necrosis occurs in both, but in Hodgkin's disease there is a more fibrinoid caseation necrosis, whereas in mycosis fungoides it is a liquefaction necrosis. The Sternberg-Reed giant cells are seen in Hodgkin's disease, but giant cells of this type are rare in mycosis fungoides.

Civatte,<sup>20</sup> MacCormac,<sup>21</sup> Durand, Cottenot and Mamou,<sup>22</sup> Lever<sup>23</sup> and others have noted similarity between mycosis fungoides and Hodg-

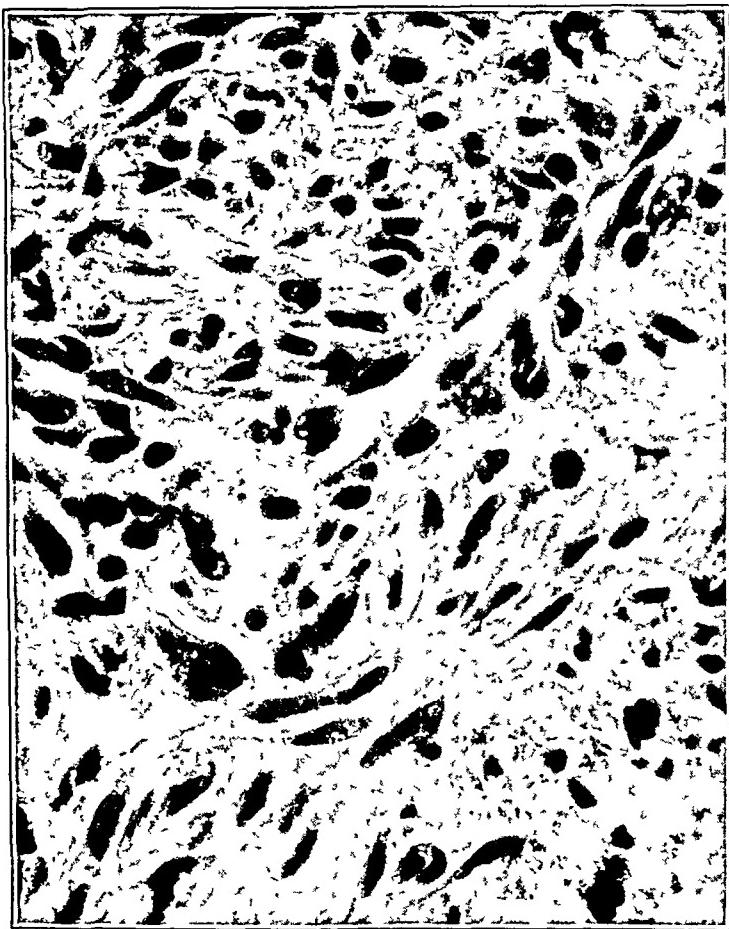


Fig. 12.—Same as figure 11. Photomicrograph showing immature as well as mature fibroblasts, new vessel formations and histiocytic reticulum cell.  $\times 650$ .

20. Civatte, A., in Darier, J.: *Nouvelle pratique dermatologique*, Paris, Masson & Cie, 1936, vol. 1, p. 266; in discussion on Touraine, A.: Lepagnole et Neret M. *reticulo-endotheliose paremycosique*, Bull. Soc. franç. de dermat. et syph. **45**:1806-1807, 1938.

21. MacCormac, H.: Mycosis Fungoides Treated by Malaria Terminating in Hodgkin's Disease. Brit. M. J. **2**:645-646, 1941.

22. Durand, H.; Cottenot, P., and Mamou, H.: Les formes cutanées ulcereuses de la maladie de Hodgkin, Presse méd. **46**:1723-1725, 1938.

23. Lever, W. F., in discussion on Mycosis Fungoides; Aplastic Anemia, Cabot Case 27352, New England J. Med. **225**:341-343. 1941.

kin's disease. This resemblance is evident because the parent tissue of the two diseases is the reticuloendothelial system. However, the preponderance of the malignant reticulum cells with the large single nucleoli is characteristic of Hodgkin's disease, whereas in mycosis fungoides this type of cell was not so numerous. In the tissue the large histiocytic cells containing a round nucleus with multiple small nucleoli and large irregular cytoplasm were most evident. Phagocytosis, karyorrhexis and pyknosis are features of mycosis fungoides which are not seen in Hodgkin's disease. However, immature reticulum cells are also seen in mycosis fungoides as in Hodgkin's disease. In some of the cases (case 2), in the terminal phases, these diseases look alike histologically, because the parent tissue is the same and because of repeated and continuous insults on this tissue it responds in both diseases ultimately in the same manner to form reticulum cell sarcoma.

Also to be considered in the differential diagnosis are leukemia cutis, multiple idiopathic hemorrhagic sarcoma (Kaposi); melanoma, dermatofibrosarcoma, lymphosarcoma and metastatic carcinoma.

In leukemia cutis characteristic features are the leonine face, purpuric subcutaneous hemorrhages and early involvement of the blood stream. Histologic characteristics are the dense cellular infiltrations, without any mitotic figures and the zone of normal connective tissue between the epidermis and the proliferating cellular infiltrations. Multiple idiopathic hemorrhagic sarcoma has proliferating fibroblastic structures together with massive extravasations of blood into the nests of proliferating fibroblasts.

Melanoma is difficult to diagnose when melanin is absent. However, the nuclei of melanoma cells are, as a rule, much smaller in relation to their cytoplasm than are those of the histiocytic reticulum cells seen in mycosis fungoides.

Dermatofibrosarcoma, although numerous mitotic figures are present, is seen to consist of intertwining bundles of fibrous connective tissue, and at all times it is monomorphous in its cellular character.

Small cell lymphosarcoma involves lymph nodes and mucous membranes primarily and is characterized by a more highly differentiated type of cell.

Metastatic carcinoma can be seen to lie in the sinusoids of the lymph nodes, compressing the medullary tissue.

#### SUMMARY AND CONCLUSIONS

Mycosis fungoides is a disease in which tumors develop which are similar to those in chronic aleukemic or leukemic monocytic leukemia. As in lymphatic or myelogenous leukemia, the cutaneous tumors are manifestations of the underlying disease.

In the disease called mycosis fungoides, the reticulum cells may differentiate into diverse types on one hand and undergo liquefaction necrosis or become malignant on the other.

Hodgkin's disease at some stages may resemble mycosis fungoides because of their common matrix, but Hodgkin's disease is at all times a malignant reticulum cell sarcoma and ends fatally.

In 1 patient with mycosis fungoides there was an associated hemorrhagic sarcoma of Kaposi, but these were two diseases entirely independent of each other.

Dr. Emil Schleicher, hematologist of Minneapolis General Hospital, assisted in the staining and diagnosing of the cutaneous imprints, and the photomicrography was done by Henry Morris, University of Minnesota.

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#### ABSTRACT OF DISCUSSION

DR. SAMUEL E. SWEITZER, Minneapolis: A discusser should have something extra to offer or have something to criticize before he starts to discuss. I have little extra to offer, and I have nothing in particular to criticize. I should like to make some observations, however, in view of the fact that Dr. Winer and I wrote a paper on Hodgkin's disease which I presented two years ago, and in looking up the literature, we noted a great deal of confusion about these two diseases. Many cases were reported as beginning mycosis fungoides and ending in Hodgkin's disease, and vice versa. So, there has been some tendency to lump these diseases into generic terms of the lymphoblastomas, on the basis that they are all varieties of the same condition.

It might be possible that this is true. However, at the University of Minnesota I and, I think, my associates are rather inclined to keep these apart until we know more about them. These cases that Dr. Winer reported today, or most of them, were from my clinic, and I think that none of you would have difficulty in making a diagnosis of mycosis fungoides. They showed typical textbook pictures. Most of us believe that it is better to keep the clinical and histologic distinctions separate, if possible, and to continue to make use of the old terms, such as Hodgkin's disease and mycosis fungoides, instead of lymphoblastoma, until we know more about the cause.

One other thought came to me as to the cause of these diseases, and digression for a moment might illustrate what I mean. Dr. Green and Dr. Bittner, of the University of Minnesota, working on the causation of mouse carcinoma—you may have heard of their observations—bred some mice, and carcinoma developed in practically all of them. But if the offspring are taken away before they have nursed over twenty-four hours, carcinoma will not develop in them. Also, if the milk is centrifuged rapidly, substances from a certain stratum of that centrifuged material can be injected into mice and so induce carcinoma in them. Dr. Green is convinced that carcinoma is due to a virus. Of course, he is a specialist in viruses, and maybe he is prejudiced.

The thought came to me that there is at least a slight possibility that the diseases, like mycosis fungoides, in which these tumors of the lymphoblastoma group are formed, might be due to a virus, because a virus can cause a wart, as Dr. Wile so well figured out many years ago, and many other diseases are caused by viruses, so that there is a possibility that a virus might cause these peculiar tumors that we group under lymphoblastomas.

DR. C. GUY LANE, Boston: I was much interested in Dr. Winer's paper because at the Massachusetts General Hospital I have followed most of the cases of mycosis fungoides for the last twenty-five years, and my colleagues and I are now reviewing some 80 cases which were recorded there over a longer period than that. We have not gone far enough to develop real statistics, but I have acquired certain impressions in that time with regard to these cases.

At one time, not so long ago, we observed that in about 20 per cent of the patients there had developed terminal changes in the blood, and in 2 of them they developed with the most rapid lymphatic leukemia that I have ever seen. In 2 other patients there developed severe terminal edema of the upper part of the body. Both of these experienced changes following the so-called spray treatment of radiation.

We have had 2 or 3 cases in which the patient was given a diagnosis in the beginning of psoriasis, and in 2 of them, as the eruption cleared up with roentgen rays, it was observed that another eruption persisted which was later determined to be psoriasis. As Dr. Winer suggested, 1 case was reported in which a rapid and terminal Kaposi sarcoma developed, a case which was reported by Dr. Greenwood and me.

In 1 other case, which I have mentioned before, the patient experienced a striking change for the better, which occurred after a streptococcal infection. This patient was seen by me in what I thought was a terminal phase. An abscess was operated on, and pure streptococcus was observed. When I saw him two months later he was 75 per cent improved, but we were not able to continue with any streptococcal vaccine developed from his culture, and he died a couple of years later.

I suppose that it is too late now to change the term mycosis fungoides to get away from the general medical conception of mycosis as a ringworm infection. I suppose that it is too late to change to granuloma fungoides or even to speak of lymphoblastoma in the fungoid stage, but it is too bad to have the disease confused with mycotic infections.

DR. HAMILTON MONTGOMERY, Rochester, Minn.: Dr. Winer has given a thorough review of the subject of mycosis fungoides. He will recall, however, some of the cases of mycosis fungoides which hemocytologists at the University of Minnesota have diagnosed as reticuloendotheliosis. I believe that the term lymphoblastoma should be preserved and that one cannot predict from the clinical appearance of mycosis fungoides whether it is that disease and is going to remain as such or whether it is going to eventuate in one of the other forms of lymphoblastoma. Some cases of mycosis fungoides remain as such, without involvement of the internal or blood-forming organs, for twenty or more years. I saw a case which clinically and histologically was mycosis fungoides of the skin, but with lymphatic leukemia in the blood and lymphosarcoma in the lymph nodes. Mycosis fungoides may also start as generalized dermatitis or erythroderma, simulating atopic dermatitis, and clear up with treatment with simple ointments only to recur after a period of months or years, with typical lesions of mycosis fungoides. It is often necessary, I believe, to make use of all diagnostic procedures, including biopsies of the skin, lymph node and, at times, bone marrow and hemocytologic studies, together with observation of the patient over a varying period before one can arrive at a diagnosis of mycosis fungoides or any other type of lymphoblastoma.

DR. HARTHER L. KEIM, Detroit: Dr. Lane has expressed some of my ideas, but, on the contrary, I do feel it is not too late. In fact, I believe that it is past time to start to do something about the term mycosis fungoides. It does not appear anywhere except in dermatologic literature, and I think that we, as derma-

tologists, are to be condemned for continuing to use it, at least without some qualifying adjective. It has been well over a hundred years since the name mycosis fungoides has been applied to this clinical syndrome.

We know, of course, that it is not mycotic, and at the present time, with roentgen ray therapy being used extensively in its management, few of the lesions fungate. It is my belief that it should be included in the group of lymphoblastomas, and until some appropriate terminology has been found we should at least refer to it as "so-called mycosis fungoides." Pathologically it is generally accepted that this syndrome is a cutaneous expression of at least three different diseases of the lymph node system, namely, Hodgkin's disease, a variety of round cell sarcoma arising from the connective tissue reticulum of the lymph nodes or elsewhere and lymphosarcoma originating in the lymphoid cells of the lymph nodes or other lymphoid structures. In short, mycosis fungoides as an independent disease does not exist.

DR. FRED W. WEIDMAN, Philadelphia: I did not hear Dr. Winer say anything about the eosinophilia that is frequently seen in granuloma fungoides and I am pleased indeed that Dr. Montgomery said what he did about the irregularity in the various features that can occur in mycosis fungoides because it repeats what I tried to indicate this morning about a possible explanation of the extremely varied clinical features which have been reported in reputed cases of eosinophilic granuloma (to be reported in the ARCHIVES OF DERMATOLOGY AND SYPHILOLOGY). In fact, I met great difficulty in diagnosing the case of Dr. Miale which was included in my series because it resembled mycosis fungoides so much, and it was only on the basis of the tremendous number of eosinophils that I (at least tentatively) included his case. I am sure that if the eosinophils had been present in smaller numbers, I would have diagnosed it as a typical example of mycosis fungoides.

Irregularities also occur in that other reticuloendothelial disease, namely, Hodgkin's disease. My study of eosinophilic granuloma indicated the necessity for studying the fat content in future investigations of both Hodgkin's disease and mycosis fungoides. As a corollary to that, with the difference that there is in the prognosis of eosinophilic granuloma and mycosis fungoides, it might be that the fat content determines that difference. After that, the introduction of fat into the picture, whether locally or systemically, might modify the course of mycosis fungoides.

Impression preparations should be routinely made in future cases of eosinophilic granuloma, as I stated this morning. For a long time they have been routine in the technic of hematologists. Such studies of bone marrow are necessary because in histologic sections there is shrinkage due to the fixative and alterations in the finer details of characteristics by which such cells as premyelocytes and monocytes may be distinguished. I have never seen in a histologic section, no matter how well it might be stained; any granules that were significant for the monocytes, and it is only by making impression preparations that one can get those ultimate and finest details which are necessary in thoroughly analyzing the hematopoiesis of so-called lymphoblastomas.

DR. LOUIS H. WINER, Minneapolis: I agree with the constructive criticisms of the terminology.

As regards the leukemic picture that Dr. Lane mentioned, Robb-Smith, in his paper on reticulum, mentioned the fact that in reticulum diseases leukemic pictures are epiphomena. We also know from clinical experience at the University of Minnesota that patients with diabetic coma may have a white cell count of lymphocytes as high as 300,000. With the diabetic coma under control, the blood picture

returns to normal within twenty-four hours. Why these patients with coma present this picture I do not know, but, anyway, a high white blood cell count is simply a pouring out of cells into the blood stream, and it can also occur in mycosis fungoides.

Dr. Montgomery and Dr. Burkhardt discussed mycosis fungoides with a monocytic leukemia picture. The monocyte in the blood is the counterpart of the reticulum cell in the tissue. A characteristic of the reticulum cell is that it can undergo liquefaction necrosis.

Dr. Weidman mentioned the eosinophilia. Jaffee, in "The Handbook of Hematology," stated that mycosis fungoides is characterized by its heavy eosinophilia. I am appreciative of Dr. Weidman's bringing out that prognostic point, because it seems that the more malignant the mycosis fungoides the fewer the number of eosinophils.

## LIPSTICK CHEILITIS

A Common Dermatosis: Report of Thirty-Two Cases

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CHEILITIS is one of the most commonly seen dermatoses in clinical practice. Among the most frequent causes of this disease in women is the dye used to impart lasting qualities to indelible lipsticks. This dye is dibromfluorescein, tribromfluorescein or tetrabromfluorescein.

Many other causative agents of cheilitis have been reported in the literature. Various authors have reported cases of cheilitis due to the following: actinic or chemically active rays of sunlight,<sup>1</sup> cold urticaria,<sup>2</sup> carmine and anilin dyes in liquid rouge,<sup>3</sup> trout,<sup>4</sup> lipstick,<sup>5</sup> methyl heptine carbonate in the perfume of lipstick,<sup>6</sup> dental plates ("hecolite"),<sup>7</sup> eosin dye in lipstick,<sup>8</sup> denture creams containing oil of anise,<sup>9</sup> lipstick in which local factors play a part,<sup>10</sup> mouth washes and cigaret holders,<sup>11</sup>

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1. Ayres, S., Jr.: Chronic Actinic Cheilitis, *J. A. M. A.* **81**:1183-1186 (Oct. 6) 1923.
  2. Duke, W. W.: Physical Allergy: Preliminary Report, *J. A. M. A.* **84**:736-740 (March 7) 1925.
  3. Miller, H. E., and Taussig, L. R.: Harmful Effects from Cosmetics, *J. A. M. A.* **84**:1999-2002 (June 27) 1925.
  4. Rowe, A. H.: Allergy in Etiology in Disease, *J. Lab. & Clin. Med.* **13**: 31-40 (Oct.) 1927.
  5. Lain, E. S.: Cosmetic Eruptions, *South. M. J.* **25**:718-722 (July) 1932.
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  7. Rattner, H.: Stomatitis Due to Sensitization of Dental Plates, *J. A. M. A.* **106**:2230-2232 (June 27) 1936.
  8. Hellier, F. F.: Lipstick Dermatitis with a Report of a Case Due to Eosin (Dye), *Brit. J. Dermat.* **49**:485-491 (Nov.) 1937.
  9. Loveman, A. B.: Stomatitis Venenata: Report of a Case of Sensitivity of Mucous Membranes and Skin to Oil of Anise, *Arch. Dermat. & Syph.* **37**:70-81 (Jan.) 1938.
  10. Baer, H. L.: Lipstick Dermatitis: An Acquired Hypersensitivity to Dye, *Urol. & Cutan. Rev.* **42**:903-909 (Dec.) 1938.
  11. Mumford, P. B.: Disorders of the Skin in the Neighborhood of Lips and Mouth, *Practitioner* **143**:612-617 (Dec.) 1939.

derivatives of bromfluorescein (with photosensitization a factor to be considered), a husband's moustache wax, amalgam fillings for teeth, toothpaste and a preparation for gums in pyorrhea ("oryl") containing oil of cinnamon and oil of cloves, orange juice and tomato juice,<sup>12</sup> tetrabromfluorescein dye in lipstick,<sup>13</sup> lipstick and an associated sensitivity,<sup>14</sup> nail polish,<sup>15</sup> certain toothpaste ("ipana" and "kolynos"),<sup>16</sup> hexylresorcinol in lozenges and in toothpaste,<sup>17</sup> lipstick in metallic containers,<sup>18</sup> Italian reed,<sup>19</sup> volatile oil such as oil of orange in bubble gum,<sup>20</sup> tetrabromfluorescein dye sensitivity (purification into five residues resulted in negative responses to the fifth residue),<sup>21</sup> again eosin dye plus photosensitization, mango rinds, tincture of krämeria,<sup>22</sup> sage tea, strong artificial lights such as carbon arc lights,<sup>23</sup> and liquid lip rouge.<sup>24</sup>

Since bromfluorescein dyes are more frequent offenders than any of the other aforementioned causes, the manufacture and the chemistry of indelible lipsticks will be discussed in this paper, and 32 cases of sensitivity to indelible lipstick dyes will be presented.

Since lipsticks are used today by more women than is any other cosmetic, it is now more important than ever that physicians be informed

12. Sulzberger, M. B., and Goodman, J.: Acquired Specific Sensitivity to Simple Chemicals: Cheilitis with Special Reference to Sensitivity to Lipstick, *Arch. Dermat. & Syph.* **37**:597-615 (April) 1938.
13. Hecht, R.; Rappaport, B., and Bloch, L.: Cheilitis, Fixed Drug Eruption and Gastrointestinal Allergy from Eosin Dye of Lipstick, *J. A. M. A.* **113**:2410 (Dec. 30) 1939.
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15. Feiler, H. B.: Eczema Venenatum Due to Lipstick and Nail Polish, *Arch. Dermat. & Syph.* **42**:224 (July) 1940.
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17. Templeton, H. J.: Cheilitis and Dermatitis Due to Resorcinol and a Derivative, *Arch. Dermat. & Syph.* **42**:138-139 (July) 1940.
18. Hathaway, J. C.: Dermatitis Caused by Lipstick in Metallic Containers, *Arch. Dermat. & Syph.* **43**:703 (April) 1941.
19. Lerner, C.: Cheilitis Caused by Italian Reed (Report of a Case), *Urol. & Cutan. Rev.* **45**:195-196 (March) 1941.
20. Miller, J.: Cheilitis from Sensitivity to Oil of Cinnamon Present in Bubble Gum, *J. A. M. A.* **116**:131-132 (Jan. 11) 1941.
21. Sulzberger, M. B., and Hecht, R.: Acquired Specific Hypersensitivity to Simple Chemicals: Further Studies on Purification of Dyes in Relation to Allergic Reaction (Cheilitis Due to Lipstick), *J. Allergy* **12**:129-137 (Jan.) 1941.
22. Urbach, E.: Allergy, New York, Grune & Stratton, Inc., 1943, p. 707.
23. Urbach, E.: Skin Diseases, Nutrition and Metabolism, New York, Grune & Stratton, Inc., 1946, p. 465.
24. Schoneberg, I. L.: Dermatitis Due to Liquid Lip Rouge, *Arch. Dermat. & Syph.* **45**:152-153 (Jan.) 1942.

of their composition. For this reason we will review the composition of commercial lipsticks as well as the lipstick without indelible dyes used in the cases described in this paper.

A good lipstick is difficult to make, because to be acceptable to the modern woman it must meet all the following specifications: 1. It should apply easily and evenly. 2. It should not be too greasy. 3. It should not "bleed." 4. It should be of proper melting point, so that it will not melt or lose its shape in hot summer weather and, at the same time, soft enough to apply evenly during the cold of winter. 5. It should not "sweat." 6. It should not crumble or crack. 7. It should have an agreeable odor and taste. 8. The colors should be uniformly blended and ground into the wax and oil base.

Lipsticks consist of a wax, fat and oil base, into which are blended oil-soluble dyes and lake colors. All colors, whether dyes or lakes (pigments), must meet standards of chemical purity prescribed by the Federal Food and Drug Administration, and each batch must be certified by that agency as meeting those standards before it can legally be used by cosmetic manufacturers. The United States Government certifies only to the chemical standards of these colors but makes no attempt to consider their allergenic properties. Sensitivity to the lake colors is rare, but sensitivity to the dyes is more frequent than is commonly realized, as we indicate later.

The waxes generally used in lipsticks are beeswax, paraffin wax, ceresin (ozokerite), carnauba wax and spermaceti.

The fats most commonly used are theobroma oil (cocoa butter), benzoinated lard, cetyl alcohol, wool fat, hydrogenated vegetable oils, petrolatum and cholesterol absorption bases.

As solvents for the waxes and fats the following oils are most often used: mineral oil, soya bean oil, peanut oil and sesame oil. Castor oil and butyl stearate are also used to dissolve the indelible bromfluorescein.

To impart odor and taste an almost endless variety of natural and synthetic flower and essential oils is used.

The lipstick prescribed for the patients with whom we are concerned in this paper contained, in addition to the certified cosmetic lake colors, white petrolatum U. S. P., liquid petrolatum U. S. P., sun-bleached depollenized beeswax and theobroma oil U. S. P. None of the lipsticks successfully used by these patients contained perfume or any halogen derivative of fluorescein.<sup>25</sup>

25. The lipstick used in this series was supplied by Ar-Ex Cosmetics, Inc., Chicago and is available now as "Ar-Ex special formula" or "now-permanent" lipstick.

*Thirty-Two Cases of Lipstick Dermatitis*

Patient	Case	Age, Years	Duration of Symptoms	Location of Lesions	Type of Lesions	Comments
D. F. ....	1	21	2 years	Lips	Fissure	Lips normal after using lipstick containing no indelible dye for 14 days
E. F. ....	2	28	12 years	Lips	Fissure, which bled at times	Lips normal after using lipstick containing no indelible dye 6 weeks
E. G. ....	3	40	2 weeks	Lips	Chapped, burning, itching, no fissures	Lips "perfect" after using lipstick with no indelible dye 3 weeks
H. K. ....	4	24	3 months	Lips	Fissure, cracks in corners	Lips normal after using lipstick with no indelible dye 10 days
R. L. ....	5	30	5 weeks	Lips	Fissures, painful	Lips completely healed after using lipstick with no indelible dye 3 weeks
E. L. ....	6	47	1 week	Lips	Fissures, edema, blisters	Lips normal; patient can use lipstick without indelible dye
S. L. ....	7	54	Several years since started to use lipstick	Lips	Fissures, burning edema	Lips normal for first time since lipstick was first used; patient uses lipstick with no indelible dye
M. M. ....	8	27	10-12 years—since started using lipstick	Lips	Fissures	After 14 days of use of lipstick containing no indelible dye lips normal
O. P. ....	9	21	1 year	Lips, mouth, neck and eyelids	Fissured lips, eruption on neck and eyelids	All fissures and eruption around neck and eyes cleared after using lipstick with no indelible dye 3 days
H. S. ....	10	26	2 months	Lips, both sides of face and chin	Lips fissured, red blotchy dermatitis on face	All symptoms completely disappeared after using lipstick containing no indelible dye for 6 days
L. W. ....	11	44	.....	Lips, chin	Fissures, lips and chin dry, cracking, irritated	All symptoms cleared after using lipstick containing no indelible dye 2 weeks
H. J. ....	12	37	4 weeks	Lips, eyelids	Lips fissured, swollen, eyelids swollen in morning	All symptoms cleared after using lipstick with no indelible dye for 1 week; when other lipsticks used, symptoms returned
R. F. ....	13	37	3 months	Lips	Fissured and bleeding in corners	After using lipstick containing no indelible dye for 30 days, lips normal
A. B. ....	14	23	6 months	Lips	Fissure, burn, peel	After using lipstick containing no indelible dye for 4 days, lips normal
J. W. ....	15	28	6 months	Lips	Fissure, edema, burn	After using lipstick containing no indelible dye for 3 weeks, lips normal

F. K. ....	16	36	Since started use of lipstick	Lips	Fissure, burning	After using lipstick containing no indelible dye for 30 days, lips normal
B. F. ....	17	52	3 months	Lips	Fissure, burning	After using lipstick containing no indelible dye for 6 weeks, lips normal
B. A. ....	18	40	1 month	Lips	Fissures	After using lipstick containing no indelible dye for 3 weeks, lips normal
E. B. ....	19	37	3 years	Lips	Fissures	After using lipstick containing no indelible dye for 5 days, lips normal
R. F. ....	20	18	Since using lipstick	Lips	Fissures	After using lipstick containing no indelible dye, lips normal
R. F. ....	21	25	2 months	Lips, face and body	Lips, fissured; face, acne; body, urticaria	After using lipstick containing no indelible dye and eliminating all perfumes all symptoms cleared
R. G. ....	22	40	10 months	Lips	Edema and pain	After using lipstick containing no indelible dye for several days, all symptoms cleared
D. L. ....	23	38	3 months	Lips	Edema	After using lipstick containing no indelible dye, lips immediately normal
A. O. ....	24	26	Several years	Lips	Fissures, edema	After using lipstick containing no indelible dye, lips normal
E. B. ....	25	18	Several years	Lips	Fissures, edema	After using lipstick containing no indelible dye and eliminating cosmetics, all symptoms cleared
M. T. ....	26	36	9 months	Lips, arms, neck, face	Fissures, dermatitis	After using lipstick containing no indelible dye and eliminating perfume and cosmetics, symptoms cleared
I. N. ....	27	17	6 months	Lips, chin, forehead	Lips, fissured; dermatitis on chin and forehead	All symptoms cleared after using lipstick containing no indelible dye
S. L. ....	28	24	Since starting to use lipstick	Lips	Dry, fissured	Symptoms cleared after using lipstick containing no indelible dye
B. M. ....	29	38	2 years	Lips	Corners cracked, lips fissured, edema and scaling	Improvement after use of lipstick containing no indelible dye; cleared completely in 2 weeks
P. S. ....	30	23	5 weeks	Lips	Edema, fissuring and scaling	After using lipstick containing no indelible dye, cleared in 1 week
E. S. ....	31	42	May 1944; seen Nov. 7, 1946	Lips	Edema, fissures	After use of nonindelible lipstick condition cleared in 1 week
M. B. ....	32	21	Dec. 1943; seen Nov. 19, 1946	Lips	Edema, fissuring and scaling; eruption about nose, eyes lacrimose and injected	After use of nonindelible dye lipstick, condition cleared in 2 weeks

Lipstick dermatitis is characterized by swelling and edema of both lips. There may also be scaling, fissuring and superficial erosions with occasional small grouped vesicles. Subjective symptoms are usually sensations of dryness, burning and tingling.

The eruption may appear after the patient has changed to a new type of lipstick, or it may suddenly appear with continued use of the same brand over a period of months or years. The precipitating factor is, of course, the idiosyncrasy to, and/or direct chemical irritation from, the indelible dyes (bromfluoresceins).

Local factors may give rise to signs and symptoms closely paralleling true cheilitis. Among the physical factors to be considered in a diagnosis of cheilitis are: trauma with contamination, salivation, light, biting or licking the lips and previous irritation of a susceptible site. The local conditions to be eliminated are: (1) herpes simplex, (2) angioneurotic edema, (3) eruptions due to drugs, (4) bullous erythema multiforme, (5) syphilitic chancres and papules, (6) leukoplakia, (7) avitaminosis, (8) eczema, (9) erysipelas, (10) malignant conditions, (11) radio-dermatitis, (12) cheilitis exfoliativa and (13) cheilitis glandularis. Generalized conditions with lip involvement to be ruled out are: (1) lupus erythematosus, (2) erythema multiforme, (3) drug eruptions, (4) pemphigus, (5) lichen planus and (6) sarcoidosis.

The 32 cases of lipstick dermatitis summarized in the table were seen in one year of private practice. The diagnosis was made on a clinical basis; confirmation of diagnosis and treatment were by elimination of bromfluorescein dyes. A lipstick was substituted which did not contain dibromfluorescein, tribromfluorescein or tetrabromfluorescein. The patients' symptoms disappeared in an average period of two weeks. The patients have remained free of symptoms to the time of writing with continued use of lipstick not containing the indelible dyes.

The factor of sensitization to light in this series of cases seems to be negligible. Only 4 of 32 patients (12.5 per cent) experienced their first symptoms in the summer. Eight (25 per cent) were vague about the seasonal onset, and the remainder (62.5 per cent) had the first attack during the winter. The patch test was not performed in this series of cases.

#### SUMMARY AND CONCLUSIONS

A list of reported causes of cheilitis and a review of the literature are presented. The chemistry of lipstick is discussed with special reference to possible sensitizers. Local and general factors in differential diagnosis of cheilitis are listed.

A series of 32 cases of lipstick cheilitis is presented, which were gathered from one year of practice. The diagnosis was made clinically, and treatment was by elimination of bromfluorescein dyes.

Photosensitization is considered negligible.

The use of lipstick with a nonindelible dye is a practical, safe and rapid treatment and the solution of this frequent cosmetic problem.

Lipstick dermatitis, or cheilitis due to chemical irritation, is much more common than is supposed and is often misdiagnosed or overlooked by the physician and by the patient.

Dr. Edward A. Oliver contributed valuable suggestions.

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## ULCERATING HEMANGIOBLASTOMA

Report of a Case

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AND

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CHRONIC ulceration of the lower extremities is one of the more common perplexing problems of medical practice. The following case is reported because of the unusual histologic observations. A thorough search of recent literature failed to reveal any comparable cases.

### REPORT OF A CASE

W. J., a Negro, aged 30, was first admitted on Jan. 15, 1932 for surgical treatment of a duodenal ulcer. Examination on admission revealed as an incidental discovery ulceration on the front of the left leg, occupying the entire mid-portion, 5 inches (12.7 cm.) in length and 2 inches (5 cm.) in width and covered by a firmly adherent brown crust. The surrounding skin was deeply pigmented. No discharge was noted. The patient stated that at the age of 9, following a blow to this region a sore developed which discharged pus and then pieces of bone. Frequently the lesion would heal over completely and then recur after any injury to this site. The Wassermann reaction of the blood was negative. Roentgenologic examination revealed condensation of the cortex of the tibia in this area. This was interpreted as an old, possibly syphilitic, osteomyelitis.

After a pyloroplasty for his duodenal ulcer the patient was not seen again until March 1938, when he applied for treatment of the ulceration of his leg. The lesion had discharged several pieces of bone intermittently during this interval. Roentgenologic examination showed little change in the condition as revealed in the previous examination. The Wassermann reaction was still negative. The lesion was treated conservatively as chronic osteomyelitis with little improvement until Nov. 15, 1939. Operation was then performed with excision of the ulcer and saucerization of the entire diseased area. At operation it was noted that the periosteum was thickened and that under it were several areas of necrotic bone; the remaining visible bone was decidedly eburnated. The entire area was curetted and a trough created, the periosteum was sutured and the wound closed. Infection set in and was cleared up by maggot therapy. Eventually (five months later), with the help of pinch grafts, the wound healed completely.

*Gross Examination of Pathologic Specimen.*—Two specimens were submitted for examination. One consisted of several flat portions of skin removed from the left leg. They had a blue-gray color and measured up to 3.5 by 0.4 cm.

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From the Departments of Laboratory and Dermatology of the Jewish Hospital of Brooklyn.

Sections fixed in Bouin's solution were taken for histologic study. Accompanying these were several irregular portions of osseous tissue removed from the tibia of the left leg. These measured up to 4 by 3 by 1.5 cm. The edges were ragged and the external surfaces showed irregular depressions. Sections fixed in 10 per cent solution of formaldehyde were taken for decalcification and histologic study.



Fig. 1.—Roentgenogram of the lesion in the tibia.

*Microscopic Examination of Pathologic Specimen.*—In a preparation from the skin the surface appeared corrugated and was covered by stratified squamous epithelium of varying thickness with superficial keratinized layers and short blunt rete pegs. The epidermis in places was irregularly acanthotic. Scattered through the upper layer of the cutis were a few small hair follicles, and in the deeper portions, some sweat glands. The papillae were broad and there was moderate interstitial edema. Throughout the preparation were sparsely placed focal infiltr-

tions of small round cells, large mononuclear cells and occasional plasma cells, mainly perivascular. Many of the large cells were laden with golden brown granules which stained blue with Perles' reaction. The striking feature, however, was the presence, within the broadened papillae, as well as in the deeper portions of the cutis, of numerous small vascular structures, singly or in groups. The lumens were narrow and the walls relatively thick. In some areas cords of cells without lumens could be seen. The lining endothelial cells were prominent. They contained large vesicular nuclei and were often clumped around rudimentary lumens. Many of the vessels were surrounded by brown pigment, coarsely granular



Fig. 2.—Photomicrograph of the lesion in the skin. Note the many small vascular structures in the papilla and in the cutis. Hematoxylin and eosin stain;  $\times 75$ .

and contained in some areas within large macrophages. This pigment stained blue with Perles' reaction. No elastic tissue could be seen with Weigert's elastic tissue stains around any of the vessels described. Preparations from the osseous tissue showed nothing of note.

*Pathologic Diagnosis.*—Skin from the left leg had sclerosing hemangioblastoma; osseous tissue from the left tibia was normal.

The history of injury and the clinical indolence of the lesion suggest an underlying abnormal type of granulation tissue with the abnormality inherent in

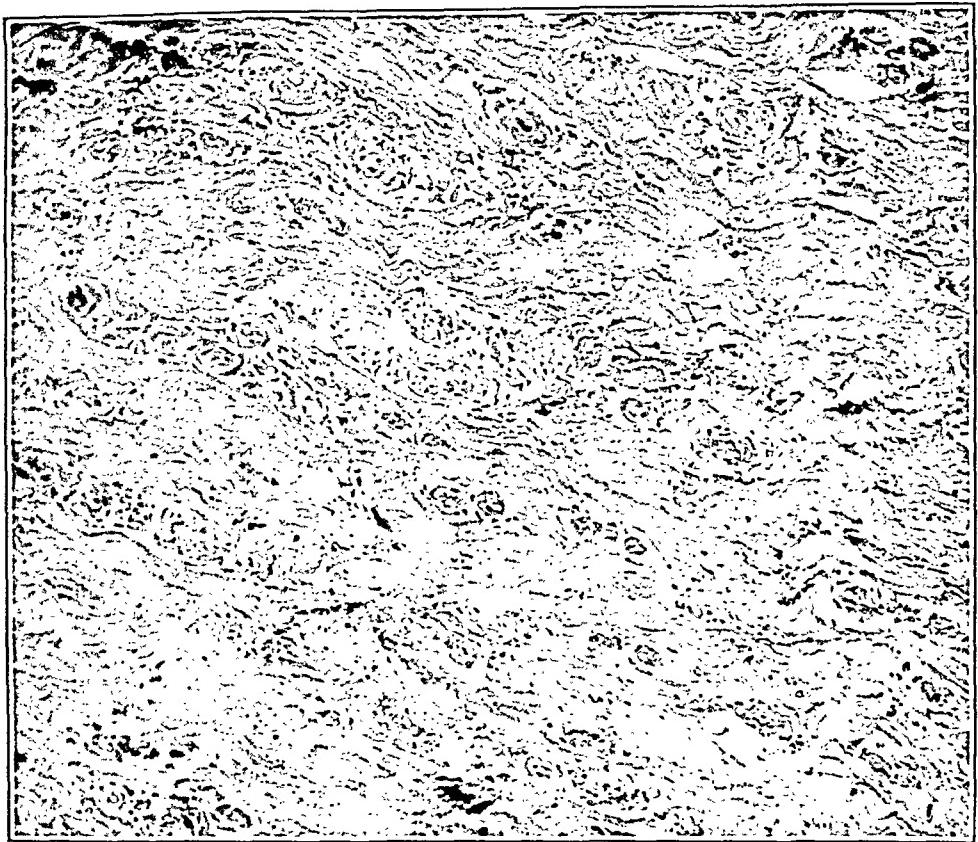


Fig. 3.—Note the vessels, many with slitlike lumens, and the pigment granules in the perivascular connective tissue. Hematoxylin and eosin stain;  $\times 150$ .

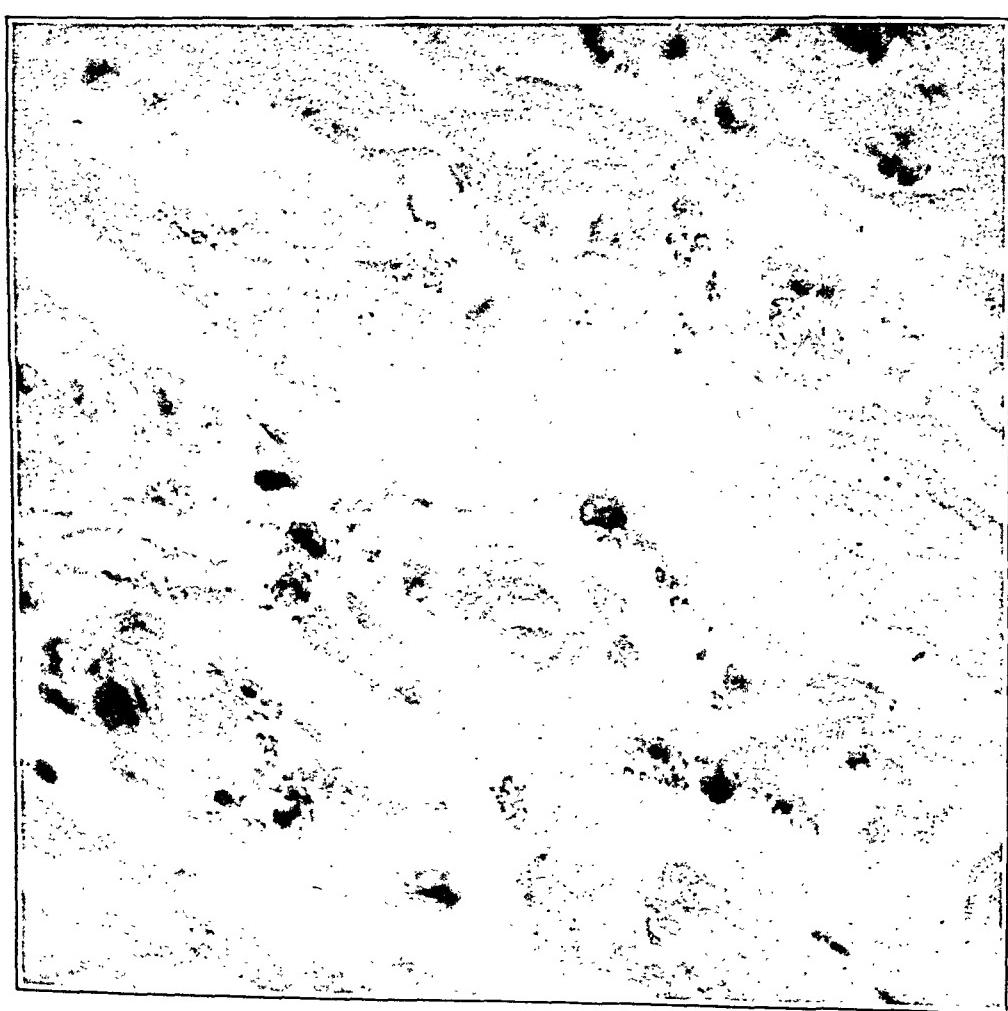


Fig. 4.—Same view as in figure 3 under greater magnification. Hematoxylin and eosin stain;  $\times 900$ .

the newly formed vessels. Whether this is a true neoplasm cannot be determined as yet. Pathologically the abnormality is demonstrated in the large cells forming the channels and also in the porosity of the new vessels as evidenced by the extravasated iron pigment lying outside their walls. Clinically the indolent erosive nature of the lesion suggests a neoplastic element.

#### SUMMARY

A chronic ulceration of the leg in an adult Negro is reported with unusual histologic observations of an abnormal type of proliferation of the blood vessels.

twenty days after the last injection resulted in slight fever. On the next day the same amount of streptomycin was injected and was followed by a cutaneous eruption over the areas of previous involvement and by an increase of eosinophils from 2 per cent to 10 per cent. The rash disappeared promptly, but the eosinophilia persisted. In another case an injection of 0.375 Gm. of streptomycin on the thirty-second day after termination of the previous treatment was followed within thirty-six hours by the reappearance of the rash. Three days later a single injection did not produce a rash, and the streptomycin was continued, but in this case the eosinophilia persisted. The report notes that the longer the interval of time between the different treatments the less likely is a second reaction. "In most instances it is well to stop the streptomycin if a skin eruption appears; certainly the dose should be reduced, and if treatment is continued it should be done with care and caution."

Mention should be made of "immediate toxic effects" in the form of "transient urticaria" of a mild or moderate character as seen by Zintel and his collaborators.<sup>3</sup> For the avoidance of this urticaria slow administration was recommended by the authors. This type of reaction seems nonspecific and cannot strictly be ascribed to streptomycin, for which reason it will not be discussed further.

A few observations on cutaneous rashes following administration of streptomycin, which we made in the summer of 1946, allowed us to come to certain conclusions that are at some variance with the opinions expressed in the report of the National Research Council<sup>2</sup> and by Heilman and his collaborators.<sup>1</sup> We think that the publication of our observations might be of practical interest in the management of treatment with streptomycin.

#### ERUPTIONS FROM STREPTOMYCIN

Among 33 patients with pulmonary tuberculosis who were treated with streptomycin, 31 were receiving 0.3 Gm. and 2 were receiving 0.5 Gm. intramuscularly every four hours. In addition, 3 of these patients were receiving 0.5 Gm. daily by nebulization. Thirty-one of the total number were male and 2 were female. Six instances of cutaneous eruption were noted. Four of the patients with eruption were receiving 0.3 Gm. every four hours, 1 was receiving 0.5 Gm. every four hours, and 1 was receiving 0.3 Gm. every four hours plus 0.5 Gm. daily by nebulization. One of the 6 patients with rash was Mexican; the others were white. All cases of rash occurred in male patients. The table shows all other particulars.

3. Zintel, H. A.; Flippin, H. F.; Nichols, A. C.; Wiley, M. M., and Rhoads, J. E.: Studies on Streptomycin in Man: I. Absorption, Distribution, Excretion, and Toxicity, Am. J. M. Sc. 210:421-430 (Oct.) 1945.

*Summary of Data Concerning Six Cases of Cutaneous Eruption from Treatment with Streptomycin for Pulmonary Tuberculosis*

Patient	Age	Diagnosis	Allergic History	Day of Onset of Rash	Character of Rash	Temperature	Eosino- phils, %	Duration of Rash, Days	Interval of Interruption of Treatment; Dosage Resumed	Duration of Further Treatment
A. Q.	21	Infiltration and cavitation of upper lobe, right lung; bronchogenic spread to upper lobe, left lung	Hay fever; mother: urticaria	7th	Generalized macular roseola, morbilliform, nonpruritic	100 F.	11	2	2 days; $\frac{1}{2}$ dose	4 mo. (completed)
C. R. A.	25	Cavitation of upper lobe, right lung; bronchogenic spread to lower lobe, left lung	None	8th	Maculopapular, particularly on upper part of trunk and on arms; nonpruritic	Normal	13	6	No interruption	4 mo. (completed)
R. R.	25	Nodular in upper lobe, right lung; minimal in apex, left lung; cavity in 1st interspace, right lung; lesion in larynx	Sister: hay fever	9th	Generalized maculopapular, follicular; pruritic	Normal	12	6	36 hr.; same dose	4 mo. (completed)
D. J. S.	22	Right lung, intracavicular with cavity	Migraine (?)	8th	Generalized macular and rubeciform, mainly on trunk	101-102 F.	21	4	No interruption	4 mo. (completed)
H. R. H.	49	Bilateral fibrous (?); tuberculosiS of urinary bladder	Hay fever	7th	Generalized, including palms and soles, erythema-multiform-like, severe pruritus	103 F.	2	3	1 day; 1/10 dose	4 mo. (completed)
E. R. C.	25	Right lung, nodular with cavities in upper lobe; bronchogenic spread to upper lobe, left lung	None	26th	Erythema-multiform-like on arms and legs; angio-neurotic edema of eyelids and lips	Normal	22	7	1 wk.; 1/10 dose	4 mo. (completed)

From the table can be seen that 3 or probably 4 of the patients had a personal or family history of allergy. In 5 patients the rash appeared on the seventh, eighth or ninth day after the commencement of the treatment. In character the eruptions were, as described by the previous observers, roseola-like, maculopapular, morbilliform, scarlatiniform, erythema-multiforme-like, urticarial, sometimes follicular, usually generalized but always more pronounced on the upper part of the trunk and on the arms; they were sometimes moderately pruritic but not so pruritic as the urticaria from penicillin. Hemorrhagic eruptions were not noted. The duration varied from two to seven days. The eruptions were apparently little influenced by treatment, which in the main was with calcium gluconate administered intravenously, "benadryl hydrochloride" N. N. R. (diphenhydramine hydrochloride) and ephedrine.

An increase in the number of eosinophils, up to 22 per cent, was present in all cases. Three patients did not show elevation of temperature. A moderate rise up to 101 to 102 F. could be observed in 2 patients. One patient had a temperature of 103 F. However, in these last 3 patients there was a return to the usual subfebrile temperatures within one day to two days. Mild to moderate toxic reactions, including nausea and tinnitus, occurred in almost all patients who were treated with streptomycin.

In 2 of the 6 cases the treatment with streptomycin was continued in spite of the rash. In the other cases it was resumed after one day, thirty-six hours, two days and one week, respectively. In 1 of these cases a single dose of 0.15 Gm. was given for the first two days. In another case one tenth of the usual dose was administered in the beginning, to be increased daily up to the normal dosage. In a third case, in which the patient had received 3 Gm. daily instead of the 1.8 Gm. which was otherwise injected, 0.05 Gm. was given on the first day, and the amount was increased by 0.1 Gm. per dose every day until the old level had been reached. In the fourth case treatment was resumed at the previous level. All 6 patients finished a full four months' course of treatment with streptomycin. In no case was there a recurrence of the cutaneous eruption, and no particular toxic or allergic reaction developed subsequently.

One more patient had cutaneous eruptions after treatment with streptomycin. This patient differed in a few aspects from the 6 discussed so far.

#### REPORT OF A CASE

A 34 year old white woman of a somewhat psychoneurotic personality had a history of eight years of hay fever. She was admitted to the hospital with a diagnosis of minimal, inactive, reinfection type of pulmonary tuberculosis of the upper lobe of the left lung. In addition, she had chronic pyelitis of the right kidney with acute exacerbations. *Bacterium coli*, *Streptococcus viridans* and

Because of their resemblance to erythema of the ninth day, as shown by the time of their eruption, by their transitoriness and by their uncharacteristic appearance, the rashes were not taken as contraindications against the continuation of the treatment. The absence of systemic reactions in all but 1 case tended to strengthen this attitude, which was further justified by the results of additional treatments that were given either without any interruption or after a discontinuation of one or two days. The full dosage could then be given, after a short transitional period, for a long time without untoward reactions. This result seems most important to us. It means that cutaneous reactions after administration of streptomycin, at least those apparently frequent eruptions of the character of erythema of the ninth day, need not deter one from the continuation of the treatment and, at the worst, should only be indications for short interruption and resumption of treatment with usually smaller gradually increasing doses.

A satisfactory explanation of the flare-up of the reaction to the Mantoux test in the 34 year old woman cannot be offered. Allergy seems out of the question, since the active agent was nonspecific. A process of the type of the Sanarelli-Shwartzman phenomenon might perhaps account for this reaction.

#### SUMMARY

Seven cases of cutaneous eruptions after treatment with streptomycin are discussed. These eruptions were, in general, of the character of the erythema of the ninth day. The allergic nature of the eruptions seemed unquestionable. Because of the mildness of the eruptions and on account of the essential absence of systemic reactions, treatment with streptomycin was continued and there were not any untoward sequelae. It is therefore suggested that eruptions of the described type should not be considered as contraindications against further necessary or desirable treatment with streptomycin.

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# DEVELOPMENT OF SQUAMOUS CELL EPITHELIOMA IN EPIDERMOLYSIS BULLOSA

Report of a Case

LAWRENCE K. HALPERN, M.D.  
ST. LOUIS

EPITHELIOMA has been known to occur in the lesions of such chronic cutaneous diseases as psoriasis, eczema, hypertrophic lichen planus and blastomycosis. The resulting tumor may be either basal or squamous cell epithelioma.

It is also well known that epithelioma may develop in scar tissue resulting from such causes as burns of varied origin, trauma, syphilis, tuberculosis, lupus vulgaris and lupus erythematosus. When scar tissue undergoes carcinomatous change it is generally of the squamous cell type. Obviously then, there is nothing startling in reporting the development of carcinomatous change in a lesion of chronic dermatosis or in cicatricial tissue. However, the case to be reported would appear to be of interest for two reasons. First, a search of the literature did not disclose a report of the occurrence of epithelioma as a sequel of epidermolysis bullosa, and, second, the development of bilateral squamous cell epithelioma of the lower extremities is rather unusual.

## REPORT OF A CASE

*History.*—O. M., a 53 year old white man, was first seen in the Skin Clinic of the Barnard Free Skin and Cancer Hospital on April 17, 1946. The patient stated that about one year previously he was struck on the right leg by a stick when he slipped off a scaffolding. The stick penetrated the skin, and a "sore" developed. This failed to heal, gradually enlarged and became somewhat painful. The ulcerated area drained a small amount of foul-smelling pus. A few months after injuring the right leg, he experienced a minor trauma to the left leg, above the heel. Apparently this was a rather insignificant injury, because the patient was unable to recall the specific details. He noticed a small "wartlike" growth, which gradually enlarged. This lesion did not ulcerate.

The patient stated that since infancy he had had blisters on the legs, dorsum of the hands and extensor surface of the elbows after slight trauma. The blisters would dry up in several days, leaving a dark red scarred area. As long as he could recall, the skin of the legs had been scarred, pigmented and scaly. The

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Studies, observations and reports from the Dermatologic Department of the Barnard Free Skin and Cancer Hospital and the Washington University School of Medicine (service of Dr. M. F. Engman Sr.).

hands were not as seriously involved as the legs. Blisters did not develop after trauma elsewhere on the body.

On being questioned regarding family history, he stated that he had a brother, aged 50 years, and a sister, aged 47 years, in both of whom blisters tended to develop on the legs, elbows and hands after slight trauma. According to the patient, their hands and legs became scarred, pigmented and scaly, but neither one experienced the ulcerating and fungating growths to be described herein. There was one other sibling, a sister, whose skin was entirely normal. His parents and all other known relatives were thought to be free from the lesions of epidermolysis bullosa. However, the accuracy of this observation is open to question.

*Physical Examination.*—The patient was in good general health. He was fairly well developed and well nourished. His height was 70 inches (177.8 cm.) and

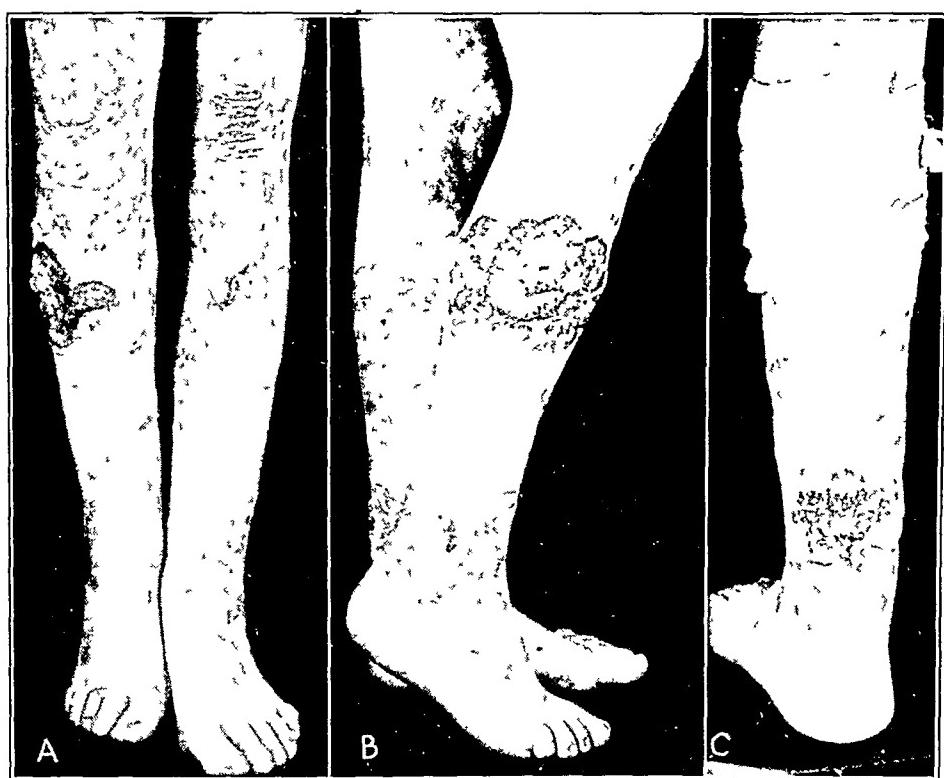


Fig. 1.—*A*, anterior view of the legs, showing scaling, scarring and squamous cell epithelioma of the right leg. *B*, lateral view of the right leg, showing large squamous cell epithelioma. *C*, posterior view of the left leg, showing squamous cell epithelioma above the heel.

weight 152 pounds (69 Kg.). Most of his teeth were missing, and the remaining teeth were infected. The liver was palpable about 5 cm. below the right costal margin. It was smooth and not tender. The remainder of the general physical examination revealed no abnormalities except as mentioned later in this report.

*Dermatologic Examination.*—Mouth: There was a superficial plaque of leukoplakia, 1 cm long, on the left corner of the lower lip.

Upper Extremities: The lesions were limited to the elbows and hands. The skin over the extensor surface of the elbows was dark red, atrophic, wrinkled and scarred. It had the appearance of cigarette paper. The skin of the dorsa of

both hands was atrophic, scarred and red. The palms were normal except for scars from electric burns experienced thirty-five years previously.

**Lower Extremities:** The lesions were limited to the legs, from the knees to the feet. The thighs were entirely clear. The skin of both legs was deep red, scarred, atrophic and scaly (fig. 1A). A few blisters were noted. The skin over the patellas was thin, atrophic and wrinkled. On the right leg, in the middle

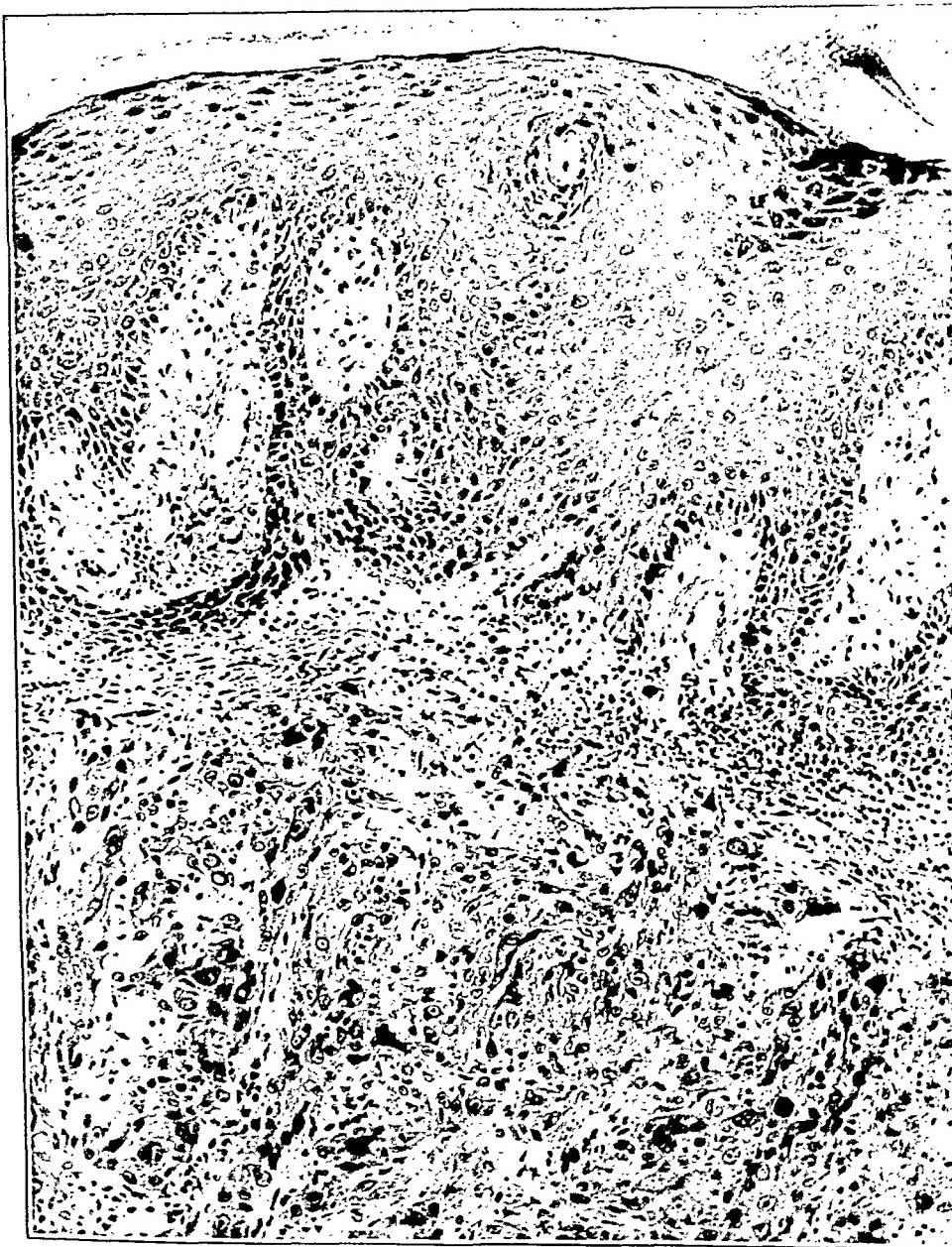


Fig. 2.—Photomicrograph of a section from the lesion on the right leg, showing squamous cell epithelioma.

third on the lateral aspect, there was a large irregularly shaped ulcer (fig. 1B). It measured approximately 20 cm. in its transverse axis and 10 cm. in its vertical axis. The edge of the lesion was hard, indurated and elevated. The center of the lesion had a moist verrucous appearance, and there was a moderate amount of foul-smelling pus and necrosis. On the left leg, about 2.5 cm. above the level of the malleoli on the posterior surface, there was a dry verrucous, hypertrophic

lesion, about 5 cm. in diameter and elevated about 1.5 cm. (fig. 1 C). It had not ulcerated. There was a hard discrete nontender lymph node, the size of an almond, in the left inguinal region and a slightly smaller one on the right side.

*Laboratory Examination.*—Urinalysis revealed no abnormality except for a slight trace of albumin. The Kahn reaction was reported negative. Examination of the blood showed the hemoglobin to be 14.5 Gm. per hundred cubic centimeters,



Fig. 3.—Photomicrograph of a section from the skin of the left leg, which was not involved by cancer. The section is stained with Weigert's elastic tissue stain and shows changes consistent with epidermolysis bullosa. The vesicle at the dermal-epidermal junction, the absence of elastic tissue in the upper portion of the dermis and the fragmentation of elastic tissue in the lower portion of the dermis may also be noted.

the red blood cell count 5,530,000, the white blood cell count 8,650 and the differential white blood cell count normal.

Roentgenologic examination of the lungs revealed them to be essentially normal, with no evidence of metastasis. Roentgenograms of the legs showed thickening and roughening of the periosteum of both tibias, but no definite evidence of metastasis.

*Histologic Examination.*—A specimen taken from the edge of the ulcer of the right leg (fig. 2) showed the epidermis to be intact, and throughout most of the section it was acanthotic. In the dermis, however, extending from just beneath the epidermis throughout the entire thickness of the corium, were islands and strands of squamous cell epithelioma. The cells making up these tumor masses were moderately well differentiated, and there were numerous epithelial pearls. Mitotic figures were numerous, and a moderate accompanying chronic inflammatory infiltrate was present. The skin that was not involved by cancer at one end of the section showed changes consistent with epidermolysis bullosa.

A specimen from the left leg through the scarred area and apparently normal skin (fig. 3) showed moderate hypertrophy in the stratum corneum, but the other layers of the epidermis were essentially unchanged. However, the rete pegs were short and stubby and in places completely obliterated. In one area a long narrow vesicle, which extended through two low power fields of the microscope, was present. It was filled with fibrin, red cells and a few leukocytes. The dermis showed moderate edema, and the blood vessels and lymph spaces were dilated. A moderate perivascular cellular infiltrate was present, which was made up of lymphocytes, plasma cells and mononuclear cells. The infiltrate was somewhat more dense immediately under the vesicle. The collagen bundles were slightly thickened, but this change was not as pronounced as that usually seen in scar tissue.

A Weigert stain for elastic tissue showed an absence of this tissue in the upper third of the dermis throughout the section. Immediately under the vesicle the absence of elastic tissue was more extensive. In the lower part of the dermis the fibers were fragmented.

In the specimen from the verrucous lesion of the left leg the section showed intense hyperkeratosis at the surface. The epidermis as a whole was extremely hyperplastic and distorted. Extending into the dermis were irregular masses of squamous cells, which were well differentiated. Only a few mitotic figures were observed. Some of the masses contained epithelial pearls. There was relatively little dermis included in the section, but a chronic inflammatory cellular infiltrate was present about the masses of squamous cells. Although the specimen was superficial, it was indicative of squamous cell epithelioma.

*Course and Treatment.*—The patient was seen in consultation by the surgical staff. Careful consideration was given to the possibility that the patient might have difficulty wearing an artificial limb because of his basic disease, epidermolysis bullosa. However, because of the size of the lesion it was recommended that the right leg be amputated and that an attempt be made to save the left leg by excision of the tumor followed by plastic repair. The patient did not consent to operation and was discharged from the hospital at his own request.

#### COMMENT

The patient presented a typical clinical picture of epidermolysis bullosa, which was confirmed by histologic observations. He sustained minor trauma to his legs and hands almost every day of his life. This usually resulted in the development of bullae, which promptly healed and were followed by scarring, pigmentation and atrophy. It may be

assumed that the severer trauma to the right leg caused an ulcer in the scarred skin, which progressed so that at the time of examination there was a well advanced and extensive squamous cell epithelioma. The verrucous lesion of the left leg, which followed only slight trauma, did not ulcerate, but showed microscopic changes consistent with early squamous cell epithelioma.

#### SUMMARY

A search of the available literature did not disclose a report of the development of cancer in lesions of epidermolysis bullosa.

A case of epidermolysis bullosa in which bilateral squamous cell epithelioma of the legs developed is presented.

Microscopically, the lesion of sporotrichosis is described by various authors<sup>2</sup> as a granuloma, consisting of a central zone of necrosis and granulation, a middle zone of epithelioid and multinucleated giant cells and a peripheral zone of lymphocytes. Polymorphonuclear leukocytic reaction is not characteristic, unless ulceration of the skin or necrosis of the lesion has occurred. Healing takes place by proliferation of connective tissue and scarring. Most authors emphasize the difficulty of detecting the organisms in tissue sections.

In 1898, Schenck<sup>3</sup> described the first case of sporotrichosis in the literature and Smith tentatively classified the organism isolated as a member of the genus *Sporotrichum*. Two years later, Hektoen and Perkins<sup>4</sup> reported another authentic case and designated the name *Sporotrichum schencki* for the organism. In practically all the recorded cases in the United States, this organism has been considered the specific causative agent.

In 1921, Warfield<sup>5</sup> reported a case of disseminated gummatus sporotrichosis in a young Negro man, in which "there was a nodule in the right lung suspected on physical examination, seen in the roentgen-ray plate and confirmed at autopsy culturally and histologically." This is the first report of such a case in this country.

Hyslop and his co-workers,<sup>6</sup> in 1926, reported a fatal case of chronic meningitis in a 15 year old white girl. The diagnosis of meningitis associated with sporotrichosis was based on the presence of spores and mycelial forms in the spinal fluid, although cultures and inoculations in animals were negative. Autopsy revealed a chronic diffuse leptomeningitis, and microscopically foci of mycelia with spore inclusions were observed in the meninges.

In 1927, Forbus<sup>7</sup> described a fatal case of pulmonary sporotrichosis in a middle-aged white woman who had had pulmonary symptoms for several years. At autopsy, cultures were taken from lesions in the lungs and *Sporotrichum* was isolated. Spore and filamentous forms of the organism were observed in smears from the lesions. The spleen was observed to contain tubercle-like nodules similar to the nodules in the lungs, but cultures were not taken and the causative agent could not be identified microscopically.

2. Forbus, W. D.: Reaction to Injury, Baltimore, Williams & Wilkins Company, 1943, p. 749. Ash, J. E., and Spitz, S.: Pathology of Tropical Diseases, Philadelphia, W. B. Saunders Company, 1945, p. 155.

3. Schenck, B. R.: Bull. Johns Hopkins Hosp. **9**:286, 1898.

4. Hektoen, L., and Perkins, C. F.: J. Exper. Med. **5**:77, 1900.

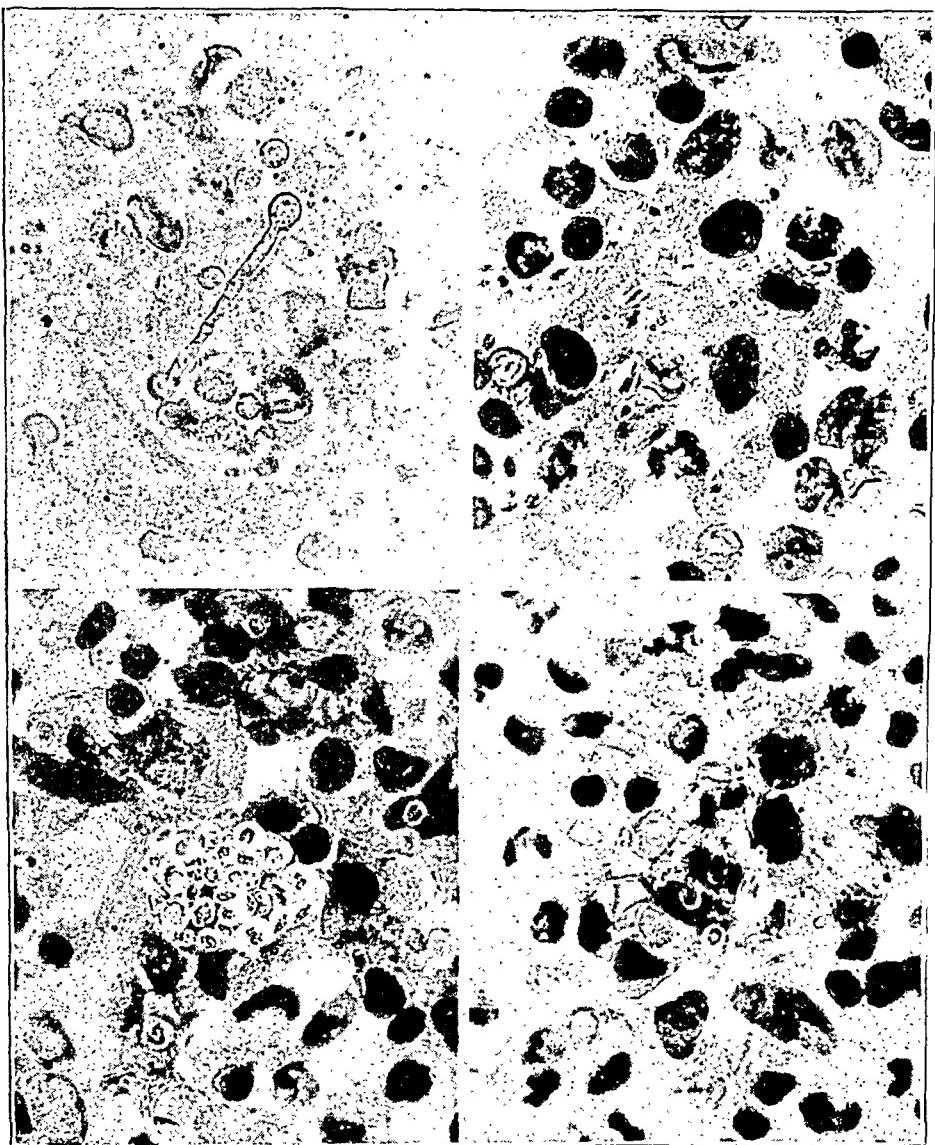
5. Warfield, L. M.: Am. J. M. Sc. **164**:72, 1922.

6. Hyslop, G. H.; Neal, J. B.; Kraus, W. M., and Hillman, O.: Am. J. M. Sc. **172**:726, 1926.

7. Forbus, W. D.: Am. Rev. Tuberc. **16**:599, 1927.

revealed increased hilar markings with an old calcification in the apex of the lower lobe of the right lung. Biopsy of cutaneous lesion showed a tuberculoid type of reaction with foreign body giant cells, epithelioid cells, plasma cells, lymphocytes and polymorphonuclear leukocytes.

*Hospital Course.*—The temperature remained within normal range throughout the entire stay in the hospital. The patient's general condition remained good up to



Photomicrographs of *Sporotrichum schenckii* in splenic pulp, reduced from initial magnifications of 1350 diameters. Upper left, *Sporotrichum schenckii* in splenic pulp in unstained sealed preparation, showing the germination of conidia, formation of a septate hypha and production of lateral and terminal conidia from it. The septum is visible just below the point of origin of the lateral conidium. Upper right, spherical, pyriform and cigar-shaped conidia in splenic pulp. Impression smear stained with hematoxylin and eosin. Lower left, cluster of yeastlike cells in impression smear of splenic pulp, showing a hyaline matrix. Lower right, portions of branched septate mycelia are visible, as well as spherical and pyriform conidia, in impression smear.

about five days before death, at which time he refused food, became weak and progressed rapidly downhill to death, on Oct. 24, 1945.

*Necropsy.*—Necropsy was performed twenty hours after death. The skin over the entire body and face exhibited numerous circular sharply demarcated ulcerations measuring 0.5 to 2 cm. in diameter. Scattered between the ulcerations were erythematous papules 2 to 3 mm. in diameter. The peritoneal cavity was lined by a smooth glistening membrane and contained 1,500 cc. of clear, yellowish brown fluid. The heart displayed moderate dilatation of the right atrium and ventricle and calcareous sclerosis of the cusps of the aortic valve. The lungs weighed 790 and 575 Gm., right and left respectively. The lower lobe of the right lung and the upper lobes of both lungs contained confluent areas of pneumonic consolidation. The symmetrically enlarged spleen, weighing 1,125 Gm., was covered by a smooth translucent tense capsule, and sections revealed a mushy, reddish tan pulp, in which the normal markings were obliterated. Attached to the tail of the pancreas was an accessory spleen, which measured 1.5 by 2 cm. The liver weighed 2,025 Gm., and its cut surface was firm, slightly congested and reddish tan. No abnormalities were observed grossly in the remaining viscera or brain.

*Microscopic Examination.*—The cutaneous lesions, which were located in the papillary corium, the reticular corium adjacent to the sebaceous and sweat glands and the subcutaneous tissue, consisted of focal areas of necrosis and a predominant cellular reaction of macrophages, which were distended with organisms. Lymphocytes were scattered between the lesions, but polymorphonuclear leukocytic reaction, formation of multinucleated giant cells and fibroblastic proliferation were absent. Many of the superficial lesions elevated and flattened the overlying epidermis, and several were ulcerated and covered with a purulent exudate.

The lymphoid follicles of the spleen were poorly defined and contained focal areas of necrosis, infiltrated with macrophages and surrounded by proliferating connective tissue in which hemosiderin was deposited. A mild reaction of polymorphonuclear leukocytes, lymphocytes and an occasional multinucleated giant cell was observed in a few of the lesions. These lesions principally involved the lymphoid follicles, but frequently extended into the adjacent pulp. Numerous organisms were disseminated throughout the spleen and were in the focal lesions both intracellularly and extracellularly and in the reticuloendothelial cells of the pulp.

Scattered throughout the liver were many submiliary foci of necrosis, which were located chiefly in the peripheral half of the lobules and were infiltrated with macrophages, lymphocytes, polymorphonuclear leukocytes and occasionally multinucleated giant cells. Organisms were present both within the macrophages and free in the tissue spaces. Other lesions, which were located chiefly around the portal triads, exhibited a minimal cellular reaction and a varying degree of fibrosis and hemosiderosis, producing a picture similar to that of early portal cirrhosis.

Miliary lesions similar to the lesions in the liver were also seen in the myocardium, the renal cortices and medullas, the suprarenal cortices and the cerebral cortex. The bone marrow, which was hyperplastic, was massively invaded by the organisms.

The other pertinent microscopic observations were acute bronchitis and lobular pneumonia, with evidence of terminal aspiration and moderate diffuse perivasculär fibrosis of the myocardium.

A fresh specimen of splenic pulp was examined and cultured by Dr. Lee Foshay, Director of the Bacteriology Service, who contributed the following information.

Examination of splenic pulp fluid under a sealed cover slip revealed numerous spherical and ovoid conidia and rare elongated ellipsoidal ones. Many spores had germinated. The presence of branched septate hyphae offered indisputable proof that growth had far exceeded the germ tube stage. Furthermore, the frequent formation of lateral and terminal conidia by a moderate number of the longer hyphae and by a few of the shorter ones offered convincing evidence of completion of the life cycle phase that is familiar on culture mediums. An example of formation of conidia by a short septate unbranched hypha is illustrated.

Impression smears of splenic pulp, stained with hematoxylin and eosin, revealed all the aforementioned features and, in addition, rare examples of the forms usually described as cigar shaped in both intracellular and extracellular locations. A striking feature of the stained smears was a clumping together of spherical, pyriform and ellipsoidal cells within what seemed to be a clear hyaline matrix. The appearance of the clumps was reminiscent of that often seen in torulosis.

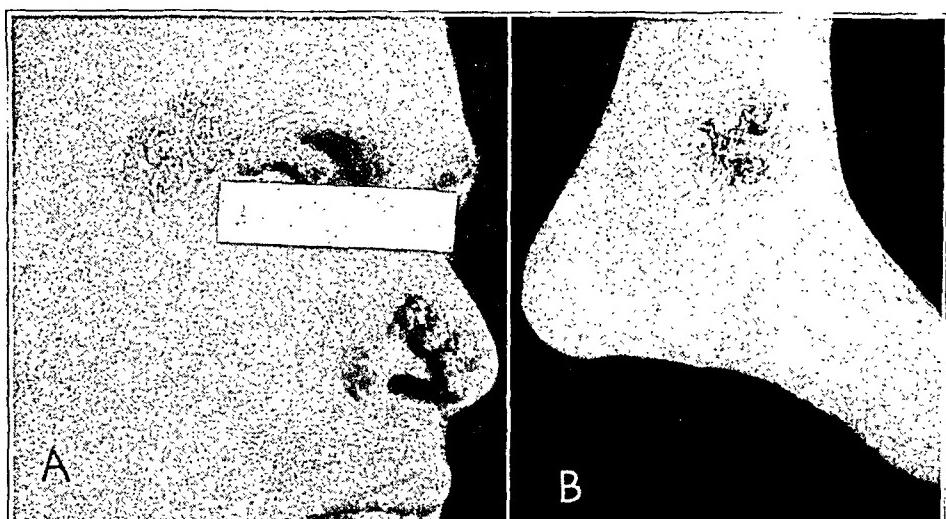
Cultures of the splenic pulp on Sabouraud's glucose agar were incubated at 37 C. and at room temperature. The former showed no growth, nor was there growth later after pure cultures were incubated at 37 C. on either Sabouraud's medium or on meat infusion agar. The cultures on Sabouraud's medium that were incubated at room temperature revealed growth after forty-eight hours. At first small and white and without aerial hyphae, the colonies grew rapidly, developed deep brown to blackish brown pigment by the fourth day and showed the characteristic convolute, or cerebriform, appearance after the fifth day. Repeated transfers of pure pigmented colonies to meat infusion agar, incubated at room temperature, always produced unpigmented colonies. Microscopic examinations of cultures showed the delicate, irregularly branched, septate hyphae with intercalated and terminal clusters of ovoid or pyriform conidia that are characteristic of *S. schencki*.

Subsequently, subcultures of the organism were examined by Conant, Moore and Emmons. All confirmed the diagnosis of *S. schencki*.

#### SUMMARY

A case of disseminated cutaneous and visceral infection with *Sporotrichum schencki* is reported in a 67 year old white man. The fatal infection began about two months prior to death with a swelling of the knee, followed five weeks later by a generalized cutaneous eruption of papular and later ulcerative lesions.

numerous microabscesses throughout the tissue, with foreign body giant cells, and round budding organisms with double refractile walls. The diagnosis was blastomycosis." During his stay at Kennedy General Hospital numerous examinations of sputum were made, but they revealed nothing of significance. The patient was treated with penicillin and sulfadiazine, and his pulmonary disease gradually cleared completely after three months of treatment. The cutaneous lesions were unimproved. A roentgenogram of the left leg showed a localized area of bone absorption at the posterior aspect of the lower part of the tibia, which was probably due to osteomyelitis. The patient was transferred to the Dermatology Center at Ashford General Hospital on Jan. 1, 1946, when I first saw him. There the observations were essentially the same as those made at Kennedy General Hospital. Roentgenograms of the chest showed the lungs to be normal, and sputum cultures disclosed no pathogenic organisms. The lesions of the face and leg continued to spread slowly. Pure cultures of *B. dermatitidis* were obtained from the lesions of the face and leg. The patient was treated with large doses of iodides, and in May 1946 the lesions were responding well to this treatment.



*A*, lesion of blastomycosis of the face; *B*, subcutaneous lesion of left ankle of same patient.

#### COMMENT

While Gilchrist's disease is limited almost entirely to the United States, the so-called European blastomycosis is observed in many parts of the world. When the latter disease affects the skin, it is often reported as Gilchrist's disease. It is possible to avoid this error in diagnosis by making cultures of the suspected organisms. In a direct smear from the lesions of each type of blastomycosis yeastlike cells with single buds are seen. When grown on blood agar at 37 C. the *B. dermatitidis* forms a pasty yeastlike culture and microscopically shows the budding forms only. On Sabouraud's agar at room temperature this organism forms a white fluffy colony. The *Cryptococcus hominis* of European blastomycosis never shows this type of mycelioid growth, but

remains yeastlike whether cultured at 37 C. or at room temperature. Other methods can be used to differentiate the organisms, but the cultural procedure is the most certain.

There are several interesting questions which arise in this case. The first question is whether the pneumonic disease was blastomycosis of the lungs, but the fact that no pathogenic fungi were isolated from the sputum tends to rule out blastomycotic involvement of the lungs. Also, the pulmonary lesions healed completely in four months with treatment with penicillin and sulfadiazine, while the cutaneous lesions persisted. The only observation in favor of a diagnosis of generalized blastomycosis was the subcutaneous lesion on the left ankle. The question whether the disease was localized or generalized blastomycosis is important in the consideration of prognosis. The latter form is nearly always fatal and the former rarely so.

Another question that arises is whether the patient contracted the disease in the United States or in England, many months previous to the appearance of the symptoms. According to the present knowledge of the disease this could not be so. The period of incubation of North American blastomycosis has been known to vary from one week to four months. Lewis and Hopper<sup>3</sup> stated that it is probably one to two weeks. This patient was in France for nearly ten months before he showed clinical signs of the disease.

Finally, the question arises as to whether the patient could have contracted the disease from a contaminated package from the United States. This is possible, but, if so, it would be the first recorded instance of transmission of blastomycosis in that manner in foreign commerce.

#### SUMMARY

The first proved case of North American blastomycosis from the European Continent is presented. The diagnosis in this case was established as North American blastomycosis, the micro-organism being differentiated from that of European blastomycosis by its characteristic culture.

9917 Euclid Avenue.

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3. Lewis, G. M., and Hopper, M. E.: An Introduction to Medical Mycology, ed. 2, Chicago, The Year Book Publishers, Inc., 1943, p. 184.

## Clinical Notes

### VERRUCOUS SPOROTRICHOSIS

LESLIE M. SMITH, M.D. and H. D. GARRETT, M.D.  
EL PASO, TEXAS

Lewis and Hopper<sup>1</sup> described six clinical types of sporotrichosis: (1) localized lymphangitic type, (2) disseminated subcutaneous type, (3) disseminated ulcerating type, (4) systemic type, (5) epidermal type and (6) a type with allergic lesions or sporotrichids.

To this classification we wish to add a seventh, namely, sporotrichotic dermatitis, a localized verrucous lesion involving both the epidermis and the corium, without subcutaneous infiltration, formation of deep nodules or abscesses, lymphangitic lesions, ulcerations, dissemination or systemic involvement.

One of us (L. M. S.)<sup>2</sup> has called attention to the varied characteristics which sporotrichosis may assume, emphasizing that one must expect to see cases of sporotrichosis which do not conform to the usual lymphangitic type, which is considered the classic picture of sporotrichosis.

The following case differs to such an extent from the usually accepted picture of the disease that it seems worthy of being recorded in the literature.

#### REPORT OF A CASE

Mrs. I. H., a Mexican housewife, aged about 40, consulted us on May 18, 1945 for a large verrucous lesion on the right cheek, the main portion of which was approximately 7 by 5 cm., with outlying satellite, superficial, pustular and verrucous lesions. The large area closely resembled blastomycosis, without deep infiltration and hardly as elevated as the usual lesion of blastomycosis. Thick material, composed of epithelial debris mixed with a small amount of pus, could be expressed from the crypts between the verrucous projections. There was no adenopathy, and the satellite lesions were only slightly infiltrated and did not suggest a lymphangitic dissemination but rather multiple autoinoculations. There was no history of exposure to thorns or shrubbery or of any other type of trauma.

The patient's general condition was excellent, and no evidence could be seen of lesions elsewhere. Curetted material and debris, obtained on pressure, failed to show any organisms on direct examination. Culture of this material, however, yielded a pure culture of a fungus which both grossly and on microscopic slide culture was typical of *Sporotrichum*.

1. Lewis, G. M., and Hopper, M. E.: An Introduction to Medical Mycology, Chicago, The Year Book Publishers, Inc., 1939.

2. Smith, L. M.: Sporotrichosis: Report of Four Clinically Atypical Cases, South. M. J. 38:505 (Aug.) 1945.

*Histologic Data.*—The epidermis showed moderate hyperkeratosis and decided irregular acanthosis, in certain areas approaching the picture of pseudoepitheliomatous hyperplasia with a tendency to whorl formation. The basal layer was intact except for one area where it was encroached on by a rather dense infiltrate beneath and the basal layer was not discernible. In the corium there was some vascular dilatation, though this feature was not so evident as has been reported by some observers. Throughout the corium and extending between the upper layer of fat cells there were large areas of dense infiltration, which consisted largely of lymphocytes with a generous admixture of plasma cells, connective tissue cells, some epithelioid cells and a few polymorphonuclear leukocytes. No miliary abscesses were seen, and no giant cells were present, although in several areas

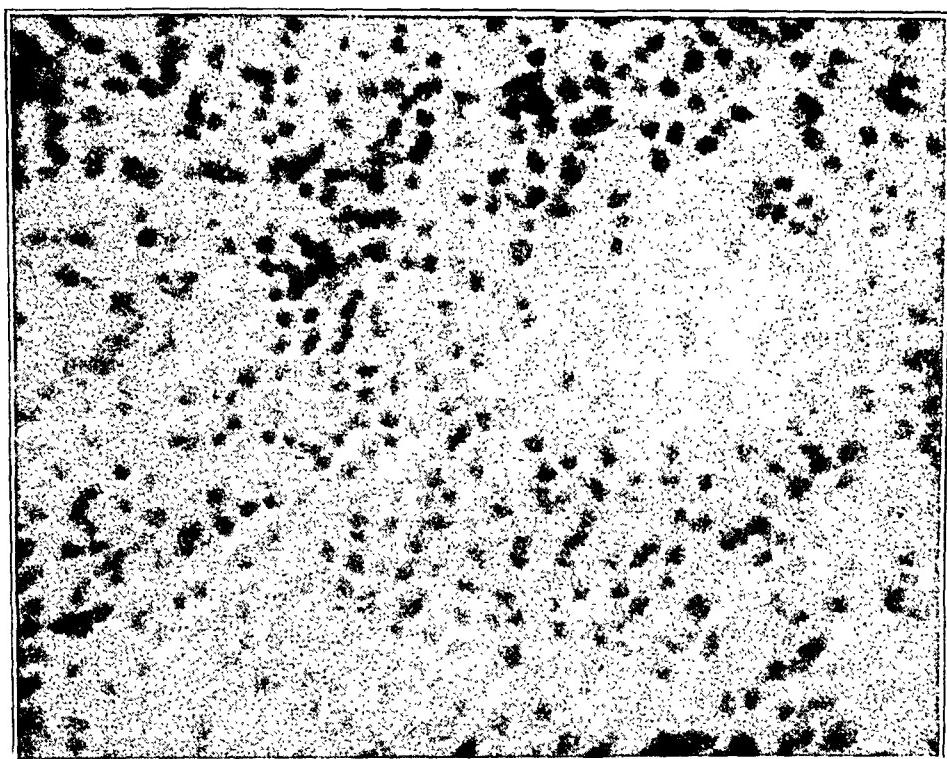


Fig. 3.—Higher power photomicrograph of cellular infiltrate in the corium.

there was an arrangement of epithelioid and round cells, somewhat suggesting the pattern of tubercles.

The lesions completely disappeared during the administration of strong solution of iodine, 15 to 45 drops daily, over a period of two months. The patient has recently been seen, approximately one year since the end of her treatment, and there has been no recurrence. Only a soft irregular slightly depressed scar remains.

#### SUMMARY

A case is presented of an unusual type of verrucous dermatitis due to *Sporotrichum*, which does not appear to conform to any of the types described in the usual classification of the disease.

Sections of hosiery are commonly employed for other parts of the extremities than those for which they were originally intended, but when over the front of the elbow they are more likely to roll up and form irritating folds.

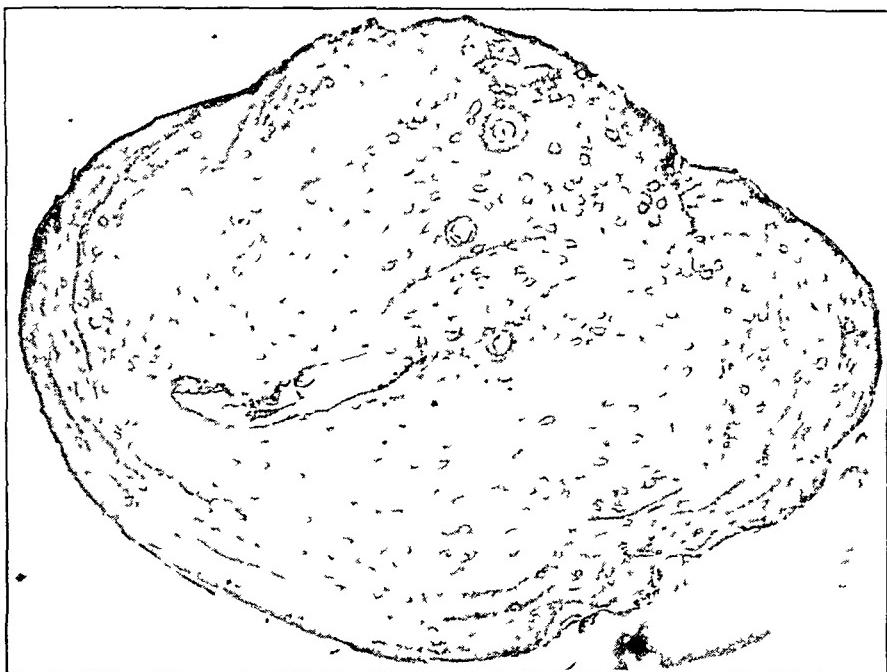
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### METAPLASIA OF BONE

Report of a Case

MAURICE J. COSTELLO, M.D.  
NEW YORK

An unmarried white woman aged 53 requested the removal of a number of milia and milium-like lesions of the face. The lesions occurred singly, on the lower half of the center of the forehead, on the cheeks, the nose and the sides of the chin. Some of them appeared to be slightly elevated, pinhead-sized to match-



Osteoblasts imbedded within an osseous matrix (low power magnification).

head-sized, nonpigmented moles, but they were hard to the touch. A grating sensation was experienced when the pointed bistoury was used to incise the skin as a preliminary step in the removal of the content of the lesions, which "popped out" in one piece. The largest of about a dozen lesions was half lentil sized, stony hard and shaped like a miniature cauliflower. The milia were of varying degrees of hardness, from what would be expected to a degree approaching the aforementioned description. This gave the impression that the lesions showing metaplasia of bone began as milia.

A specimen studied by Dr. Fred D. Weidman showed that "the epidermis had become detached from the rest of the specimen, and none of the architecture of the skin was submitted for study. What there was had the structure of bone, with typical osteoblasts embedded within a pink osseous matrix. Calcification appeared only in the form of shreds of blue granules which were patterned as

The patient, a 63 year old man, had an epithelioma on the cheek (fig., A), which on histologic examination was found to be of the mixed cell type. He was treated with roentgen rays, receiving 2,160 r once each week for three weeks. The site healed within the course of eight weeks, and when examined several weeks later there was an atrophic scar with slight depigmentation, around which blackish horny lesions were arranged in a concentric zone (fig., B). On compression with a comedo extractor, each of the horny plugs was found to be a

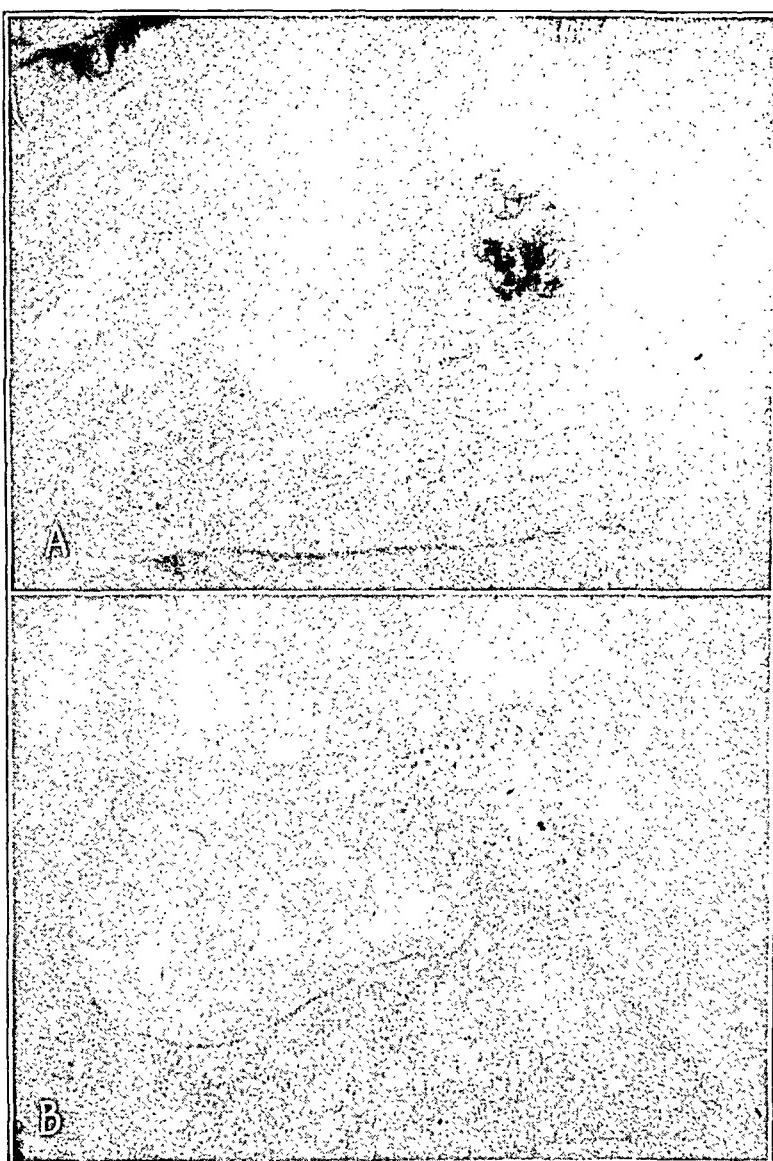


Fig. 1.—A, mixed cell epithelioma of the face. B, comedos surrounding the roentgen ray scar.

comedo. In the section of the illustration showing the lesion as it was before treatment, there is no evidence of comedos.

This lesion constitutes a clinical curiosity unique in my experience and has no other significance. I have been unable to find a report of any similar case in the literature which is available to me.

Ormsby and Montgomery<sup>1</sup> stated that the comedo is due to hyperkeratosis occurring about the neck of the follicle, causing retention of the fatty material which should ordinarily be thrown off. It is believed that irritation induced by the microbacillus of Unna and Sabouraud is usually the cause of hyperkeratosis. Others have associated the formation of comedos with folliculitis resulting from infection. At times, as in some cases of grouped comedos, the irritant is found in chemicals such as oils (e. g., Brilliantine or camphorated oil). Becker and Obermayer<sup>2</sup> stated that comedos are occasionally seen about the eyelids in elderly persons and must be interpreted as senile phenomena. In fact, it is most likely that any type of reflex or local disturbance which would tend to increase the activity of the sebaceous glands may lead to the formation of comedos. The most frequent form is that seen associated with acne vulgaris.

These facts are pertinent in this case: 1. The patient was beyond the age at which acne occurs. 2. There was no evidence of comedos before roentgen therapy. 3. The comedos appeared in the zone beyond the healed scar. Therefore, it is assumed that the comedos in this case were due to an irritation of the follicles of the sebaceous glands immediately surrounding the roentgen ray scar, and it is presumed that it represents a compensatory hypertrophy of the sebaceous apparatus.

30 North Michigan Avenue.

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1. Ormsby, O. S., and Montgomery, H.: Diseases of the Skin, Philadelphia, Lea & Febiger, 1943, p. 1215.

2. Becker, S. W., and Obermayer, M.: Modern Dermatology and Syphilology, Philadelphia, J. B. Lippincott Company, 1940, p. 521.

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#### RESULTS OF REPEATED EPILATION WITH ROENTGEN RAYS IN TINEA TONSURANS

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WASHINGTON, D. C.

In the past thirty years some 500 children with tinea tonsurans have been treated with the roentgen ray in the office. The standard five point exposure method has usually been employed,<sup>1</sup> although occasionally a four point exposure system has been used. Certain of these children had more than one treatment, and as there are certain hazards connected with this it seems wise to point them out, since the disease has become so prevalent over much of the country.

Thirty of the children had two roentgen ray epilations, and in every instance the regrowth of hair was satisfactory. The interval between the two treatments was in each case not less than three months. The second treatments were necessary because of reinfections, which occurred in orphan asylums of some type. Five Negro boys, inmates of the City Orphanage at Blue Plains, were each treated three times within fifteen months. This was due to error on the part of a too zealous institutional attendant. The boys varied in age from 8 to 11 years, and all were affected by the human type of ringworm. Following the second epilation the regrowth of hair was satisfactory, as in MacKee's<sup>2</sup> experience, but after

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1. Hazen, H. H.: X-Ray Treatment of Tinea Tonsurans, *J. Cutan. Dis.* **37**: 307, 1919.

2. MacKee, G. M.: X-Rays and Radium in the Treatment of Diseases of the Skin, ed. 3, Philadelphia, Lea & Febiger, 1938, p. 469.

the third treatment the hair did not reappear for at least three months, and then it was dry and uniformly scanty. As nearly as could be estimated, between one third and one half of the hair reappeared. Many of the hairs showed alternate rings of white and black, sometimes as many as six to a hair, about half an inch (1.27 cm.) in length. Some two years later 3 of these boys were seen again, and none had shown any improvement. It is worthy of note that all patients were treated with the same apparatus and by the same operator, and that they were not all treated on the same day.

Judging from these observations it would seem that while two standard roentgen ray epilations are perfectly safe, a third should never be done.

1911 R Street, N. W.

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### PILI TORTI

#### Report of a Case

WILLIAM M. SISKIND, M.D.  
NEW YORK

Pili torti is a rare disease of the hair; the pathogenesis is unknown, and the treatment is unsatisfactory. Pili torti is usually considered a congenital disease. In Ormsby and Mitchell's<sup>1</sup> case the disease had been present at birth, with a slight growth of hair when the child was 14 months; they stressed the resemblance to monilethrix. In Ronchese's<sup>2</sup> case it was also of congenital origin, other members of the family being similarly affected. His patient improved with the application of hydrous wool fat to the scalp.

Clarke and Glicksberg<sup>3</sup> reported a case of a 14 year old boy who had been completely without hair until 5 years of age. Investigation of the endocrine system revealed no abnormalities. The association with keratosis pilaris and also monilethrix has been reported.

#### REPORT OF A CASE

R. Z.,<sup>4</sup> aged 17, presented herself in January 1946, complaining of extreme shortness and brittleness of the hair of the scalp, with loss of hair in several areas.

*History.*—The patient had a normal birth and development, with no serious diseases of childhood until 1940, when she had a severe attack of scarlet fever. After this she noticed that her hair was brittle, did not grow to its former length and had lost its luster. Small patches of baldness also developed on the top and sides of the head. She has not cut her hair since her illness six years previous to the time of consultation.

She has one brother, whose hair is curly but grows normally. Her father and mother have no disease of the hair.

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1. Ormsby, O. S., and Mitchell, J. H.: Atrophy Pilorum Monilethrix, Arch. Dermat. & Syph. **10**:393-394 (Sept.) 1924.

2. Ronchese, F.: Twisted Hairs (Pili Torti), Arch. Dermat. & Syph. **26**:98-109 (July) 1932.

3. Clarke, G. E., and Glicksberg, E. L.: Pili Torti: Report of Case, Arch. Dermat. & Syph. **43**:836-838 (May) 1941.

4. This patient was presented before Manhattan Dermatological Society and reported by Wise, F.: A Case for Diagnosis (Pili Torti), Arch. Dermat. & Syph. **45**:1183-1184 (June) 1942.

## Society Transactions

### NEW YORK ACADEMY OF MEDICINE, SECTION OF Dermatology AND SYPHILIS

Levis B. Robinson, M.D., *Chairman*

Samuel M. Peck, M.D., *Secretary*

Nov. 12, 1945

Papulonecrotic Tuberculid. Presented by DR. FREDERICK REISS.

F. C., a woman aged 33, was first observed in the dermatologic clinic of the New York Hospital on Oct. 21, 1937 with erythema induratum, which subsequently healed. At that time the patient was being treated for advanced pulmonary tuberculosis with bilateral pneumothorax. She returned in September 1945 with lesions on the lobe of the right ear and the scalp, of six months' duration.

On the lobe of the right ear there are two depressed, hyperpigmented scars and three or four inflamed papules with a necrotic top. Several similar lesions are scattered over the scalp. There are no changes on the extremities.

Roentgenographic examination on Oct. 5, 1945 gave evidence of residual pleural thickening throughout both sides of the thorax, more noticeable in the apices, from reexpansion after pneumothorax, and a fibrocalcific tuberculous process in the upper lobe of the right lung and a few fibrous scars in the upper lobe of the left lung.

The erythrocytic sedimentation rate was 10 mm. in one hour. A smear of the sputum was negative for acid-fast bacilli. A test with old tuberculin in a dilution of 1:1,000 gave a necrotic papule in forty-eight hours, with a surrounding erythematous area of 6 cm. The Wassermann reaction of the blood was negative.

Biopsy showed the epidermis to be thick and flattened, disintegrated in some places and replaced by a scab of polymorphonuclear leukocytes. The corium was dense and fibrous and was invaded by a large number of leukocytes, most of which were polymorphonuclear forms. Part of the collagenous tissue had undergone coagulation necrosis, but there was no sign of tuberculoid structure. It was felt that this stage of the histologic changes might represent an early acute, nonspecific reaction to tuberculotoxins.

#### DISCUSSION

DR. E. W. ABRAMOWITZ: From the appearance of the lesions on the scalp, one would suspect lupus erythematosus. The lesion on the ear may be a giant-sized papulonecrotic tuberculid. I have seen such a lesion, although it is unusual. The patient will bear watching for other signs of lupus erythematosus or papulonecrotic tuberculid, and I believe that another biopsy is indicated.

DR. FREDERICK REISS: I feel exactly as Dr. Abramowitz does. If he had seen the patient eight weeks ago, he would have been confronted with the same puzzle. I still think there are cases in which papulonecrotic tuberculid follows the course in this case. However, the lesions on the scalp are somewhat suggestive of lupus erythematosus.

**Scleroderma.** Presented by DR. MABEL SILVERBERG.

M. H., a girl aged 9, was first observed in the dermatologic clinic of the New York Hospital on Dec. 22, 1943. The child had had chickenpox but no other diseases. Four years ago it was noted on routine examination that the patient's face was somewhat puffy. One year later the right cheek appeared swollen and bluish red. The area was sharply demarcated. The left cheek also appeared somewhat red and puffy at this time. Six months later the right lower eyelid, the right side of the nose, the right cheek and the right temporal region were distinctly indurated and showed areas of an ivory white color. The lashes of the right lower lid had fallen out.

The skin of the face on the right side in the temporal area and over the right cheek, the right lower eyelid and the right side of the nose is depressed and hide-bound and varies in color from an ivory white to a mottled tan. There are three areas of pronounced induration the size of a quarter. Alopecia of the right lower lid is present. The mottled brownish discoloration extends over the chin, which, however, is not indurated.

The urine was normal on frequent examinations. The blood count on Dec. 14, 1943 showed 12 Gm. of hemoglobin per hundred cubic centimeters, 4,580,000 red cells and 7,800 white cells, with 50 per cent lymphocytes, 45 per cent polymorphonuclear leukocytes, 3 per cent eosinophils and 2 per cent monocytes. The count on Aug. 21, 1944 showed 12 Gm. of hemoglobin, 4,480,000 red cells and 6,000 white cells, with 72 per cent lymphocytes, 25 per cent polymorphonuclear leukocytes, 2 per cent eosinophils and 1 per cent monocytes. The Wassermann reaction of the blood was negative on Oct. 5, 1942. On Sept. 5, 1944 the Wassermann reaction of the blood was negative and the Mazzini reaction doubtful. The serum calcium was 12 mg. per hundred cubic centimeters on Oct. 6, 1944. Roentgenograms of the sinuses and teeth were normal.

Treatment has consisted of daily massage with hydrous wool fat. The patient is presented for therapeutic suggestions.

**DISCUSSION**

**DR. EUGENE T. BERNSTEIN:** I think the case is one of hemiatrophy facialis, a disease based on trophic disturbances affecting the muscles, tissues and bony structures. Scleroderma-like changes are also seen in this case, but the entire half of the face is in a state of atrophy. There is also involvement of the bony structure. There is a spot on the eyelid which one cannot pick up with the fingers, but otherwise the skin is freely movable. I think it is justifiable to place this case in the category of hemiatrophy facialis.

**DR. FRANK VERO:** I agree with Dr. Bernstein in the diagnosis of hemiatrophy, which is often associated with scleroderma.

**DR. SAMUEL M. PECK:** I also agree with Dr. Bernstein that there is not only a cutaneous atrophy but also involvement of the underlying subcutaneous tissue, as well as the muscles, on that side. The disease was described by Kartagener and myself in 1928 (*Dermat. Ztschr.* 52:81, 1928). In the case we reported there were both hyperpigmentation and depigmentation, as well as loss of hair. Later, I saw 2 other cases in which the lesions were of the same type, 1 in a male and the other in a female. The results of treatment in all my cases were very poor.

DR. FRED WISE: Does the case which Dr. Peck has just described come under the same category as *coup de sabre*?

DR. MABEL SILVERBERG: I am not sure whether there is atrophy of bone in the present case, although there appears to be. I first saw the child in the edematous stage, when there was no atrophy, then the eyelid became involved with typical scleroderma. There was no doubt of scleroderma at the onset, and atrophy of the bone, if present, developed later.

### Scleroderma; Tropic Ulcers; Calcified Ganglion of Tendon Sheath.

Presented by DR. MABEL SILVERBERG.

M. T., a man aged 56, Jewish, born in Austria, first came to the New York Hospital on June 21, 1945. Stiffness of the skin had gradually become more noticeable during the preceding eight years, although he was not aware that his condition differed from the normal. His reason for consulting a physician was the pain from ulcers on the outer side of each foot. These ulcers were treated by his physician with local medication and finally with fulguration. Foot baths were prescribed but did not help. Some healing has resulted from the local use of penicillin ointment. He states that cold weather does not bother him.

The face and extremities show hidebound skin, with absence of wrinkling and considerable immobility. Perforating ulcers are present on the outer side of each foot. A cystic lesion on the back of the left hand (ganglion of a tendon sheath?) is hard to the touch and is thought to be partially calcified. Scattered over the thighs and other parts of the body are brown maculopapules. Histologic section of one of these lesions revealed typical sclerodermic changes. The Mazzini test gave a negative reaction. The basal metabolic rate was —2 per cent.

### DISCUSSION

DR. FRED WISE: My associates and I have used dihydrotachysterol in our clinic for the past five years, without obtaining any definite responses that we could ascribe to its use. Dr. George C. Andrews, at the last meeting of the New York Dermatological Society, mentioned 2 cases of progressive scleroderma treated with injections of penicillin, with pronounced improvement. Since dihydrotachysterol is a relatively harmless drug, it should be given a trial in cases of progressive scleroderma.

DR. SAMUEL M. PECK: When dihydrotachysterol was first suggested as a therapeutic agent for scleroderma, it was eagerly seized on by most dermatologists. However, it was soon realized that, although some benefit was to be derived from its use in the edematous stage of the disease, the drug, as was to be expected, had no effect on the atrophic end stage. Neither has it been my experience that this drug is able to halt the course of progressive scleroderma. One must be cautious in evaluating the results of therapy of scleroderma in the edematous stage. This stage tends to run its course, and at the end of this period, just before the more serious atrophic stage becomes manifest, the patient actually feels better; if the hand is involved, there is ability to move the fingers more easily. This apparent improvement might lead to the erroneous conclusion that the course of the disease is influenced by whatever therapy is being carried out at that time. Unless one is to conclude that scleroderma is due to a focus of infection or is an infectious process, I cannot understand why penicillin should be successful in treatment of this disease. In cases of scleroderma with dermatomyositis one might have better results with penicillin, for it has been my impression that the latter process was infectious in character.

The Mazzini test was negative on Sept. 27, 1945. A blood count on October 2 showed: hemoglobin content 9.7 Gm. per hundred cubic centimeters, 3,800,000 red blood cells, normal platelets, and 6,800 white blood cells, with 50 per cent lymphocytes, 48 per cent polymorphonuclear leukocytes, 2 per cent eosinophils and no monocytes or basophils. A blood smear showed slight achromia. The corrected sedimentation index was 0.3; the total fall was 0.5 mm. in one hour; the red cell volume was 38 per cent.

Histologic examination showed a moderate amount of parakeratosis and hyperkeratosis, affecting especially the follicular orifices. There were thickening of the epidermis and moderately copious sleeves of lymphocytes about the vessels of the derma and in the neighborhood of the hair follicles. Melanophores were not present in the cutis. There was no basophilic degeneration.

#### DISCUSSION

DR. BEATRICE M. KESTEN: I do not know what this eruption is. It might be well for us to have a clinic and present the variety of pigmentations seen in the Negro skin. We could then clear up the terminology.

DR. SAMUEL M. PECK: There is one objection to the diagnosis of pigmentary dermatosis in this case, and that is the fact that one is dealing with a colored skin. In an inflammatory process a colored skin acts differently from a white skin; i. e., it becomes pigmented or depigmented. There seems to be atrophy in some of the lesions, but I should hesitate to label the disease as pigmentary dermatosis. Even acne will often cause pigmentation in a colored skin.

DR. EUGENE T. BERNSTEIN: I think a diagnosis of Riehl's melanosis should be established here. This dermatosis affects the face in exactly the locations seen in this case. I think poikiloderma occurs more frequently on the neck.

DR. FREDERICK REISS: I believe that in Riehl's melanosis the pigment is more diffuse, and not lichenoid, as in this case. I am not quite convinced that this case represents the Hoffmann-Habermann type of melanosis, but that is the most nearly suitable diagnosis that I could suggest.

#### A Case for Diagnosis (Parapsoriasis?). Presented by DR. THOMAS N. GRAHAM.

E. K., a white woman aged 66, was first seen in the dermatologic clinic of New York Hospital on Dec. 1, 1941, complaining of a generalized, slightly scaly eruption, with very little itching, which had been present for four years. The histologic diagnosis at that time was "cutaneous lesion resembling both parapsoriasis and pityriasis rosea." The patient returned on Oct. 10, 1945, at which time her eruption was essentially the same as on her previous visit.

Most of the cutaneous surface shows an erythematous, macular eruption, with "branny" scaling. On the anterior surface of the chest and neck there are dilated blood vessels, which suggest poikiloderma vasculare atrophicans. There are also a number of violaceous papules on the neck. Numerous erythematous, small, follicular papules occur on the arms.

The Mazzini test of the blood gave a negative reaction on Aug. 9, 1945. The blood chemistry was essentially normal. The urine was normal. A blood count showed 10.5 Gm. of hemoglobin, per hundred cubic centimeters, 3,200,000 red cells, normal platelets and 5,000 white cells, with 59 per cent polymorphonuclear leukocytes, mature form, 6 per cent band cells, 30 per cent lymphocytes, 2 per cent monocytes, 3 per cent eosinophils and no basophils.

Biopsy showed general flattening and thickening of the epidermis, a well marked, but somewhat interrupted, granular layer and a fibrous and thickened derma with sleeves of lymphocytes about the vessels. There was rather conspicuous cavitation of the cells of the rete malpighii, but no parakeratosis was noted and little keratosis. The picture was thoroughly equivocal; in the absence of parakeratosis, it was more similar to that of parapsoriasis *en plaque*. The basal layer was scarcely recognizable, a characteristic of parapsoriasis; so the diagnosis is questionable parapsoriasis *en plaque*.

#### DISCUSSION

DR. FRED WISE: The reticulated eruption gives the impression of parakeratosis variegata, described by Unna, Santi and Pollitzer.

DR. EUGENE T. BERNSTEIN: I suggest the diagnosis of seborrheic dermatitis. The patient has scaliness and dandruff of the scalp. I do not think the eruption is parapsoriasis.

**Tinea Capitis Due to Microsporon Audouini.** Presented by DR. MARGARET KLUMPP and DR. FREDERICK REISS.

M. P., a married white woman aged 32, was first observed in the dermatologic clinic of the New York Hospital on Feb. 23, 1944. The patient had two small children attending the clinic for treatment of *M. audouini* infection of the scalp. She called our attention to her scalp because of itching. Examination with Wood's light showed several patches of fluorescent hairs scattered over the scalp, and cultures revealed *M. audouini*. The patient had had alopecia areata several years ago, with no return of the hair. She had smooth, noninflammatory areas of alopecia involving chiefly the posterior hair line and extending upward about 2 inches (5 cm.) from this level. In addition, there was complete loss of the eyebrows and eyelashes. Otherwise, there was nothing unusual in the patient's history or examination.

Manual epilation and application of 10 per cent ammoniated mercury U. S. P. proved of no avail, and it was decided to administer estrogen by mouth. It was given in the form of mestilbol N. N.R. ("monomestrol tablets") 2 mg. daily, in the second half of the menstrual cycle, the dose being later increased to 2.5 mg. a day. This medication was repeated during each cycle from May through July 1944. Thereafter, estrogenic substances N. N. R. ("premarin"), 2 tablets (0.63 mg. each) daily, was given from July through September 1944. During this time there was no improvement in the status of the infection. Subsequently, local epilation with roentgen irradiation was performed, and the affected areas treated with 6 per cent sulfur and 3 per cent salicylic acid. Since it was assumed that the oral medication with estrogen preparations could not raise the hormone level of the blood to such an extent as to produce an adequate concentration in the affected areas, it was considered advisable to apply stilbestrol, 0.04 per cent in an aerosol base, locally. After this treatment the infected hairs became loose and could easily be pulled out, whereas prior to the treatment this had been almost impossible without breaking the hair. The infected area also became smaller, but many infected hairs were still present, as judged by their fluorescence under Wood's light. It may be added that local application of methyl testosterone, 5 mg. daily, was made for about two weeks, without appreciable benefit. For another two weeks thyroxin, 0.01 per cent in an aerosol base, was applied, resulting only in easier manual epilation. At present there are still many foci of fluorescent hair.

Cultures of material from the scalp yielded *M. audouini*. The urine was normal. The Mazzini reaction of the blood was negative. The basal metabolic rate was —8 per cent. The cholesterol of the blood was 318 mg. per hundred cubic centimeters. Vaginal smears showed a "normal cycle," as read by Dr. E. Shorr.

#### DISCUSSION

DR. MARION B. SULZBERGER: It is an understatement to say that this infection is relatively rare. It is most unusual to find a proved case of infection of the scalp with *M. audouini* in an adult. I do not recall having seen such a case and have heard of only 1 or 2 instances. Its presence in this case means that the woman has an anomaly which makes her scalp and hair like that of a child with respect to susceptibility to infection with *M. audouini*. While it appears logical to make these therapeutic approaches with endocrine products, the treatment has had notable lack of success in children. Androgens and estrogens have been administered, both systemically and locally, in almost every form, natural and synthetic, to the point of producing artificial puberty; and one may say that none of these procedures has proved of any value. While there is a remote possibility that an adult might react differently from a child, the results reported indicate that here, too, administration of these hormones has failed. I hope I am not "jumping the gun" by telling you that Dr. Stephan Rothman, of Chicago, has been making studies on the nature of the difference between adults' and children's hair, which will shortly be published. Dr. Rothman has isolated a factor from adults' hair which kills *M. audouini* and which is not present in children's hair before puberty.

DR. BEATRICE M. KESTEN: I wonder whether we are not simply accepting this idea of the rarity of fungous infections in adults. Perhaps if one were to examine the mothers who come in with infected children, more cases of *tinea capitis* would be found in adults.

DR. SAMUEL M. PECK: I should like to subscribe to Dr. Kesten's suggestion. I have seen girls and boys past the age of puberty, 16 years or older, who acquired their infections with *M. audouini* before puberty and still showed persistent infection of the scalp. C. H. Danforth, in his monograph on "Hair," published in 1925, pointed out that the scalp during the first few years of childhood becomes coarser and the average diameter of the hairs approaches that of the adult hair. Most of the coarse hairs of young children are without a medulla, although an occasional hair with an interrupted, or even continuous, medulla may be found from an early age. After puberty the number of hairs with a medulla increases, but in general there are many hairs, even in old age, which still lack the medulla. Consequently, if one were to stick closely to the definition of a terminal hair as one containing a medulla, it would be necessary to regard a considerable part of the hair of the head as transitional. If the structure of the adult hair is the reason that adults seem to be resistant to infection with *M. audouini*, perhaps it is these transitional hairs, still retaining the childhood structure, which, if they are in predominance, would account for the persistence of some of the postpuberty infections. However, that is not my conception of why adults seem to be resistant to infections of the scalp with *M. audouini*. My collaborators and I, as well as others, have pointed out that the sweat glands play an important role in fungous disease by contributing to the secretion of substances which are fungistatic. Perhaps in adult life the glands of the scalp also secrete a substance which helps to control infections of the scalp. I was interested in Dr. Sulzberger's comment that Rothman has isolated from adult hair a substance which is lacking in the hair of children and which may account

for the resistance to infection of adult hair. However, I wonder whether Dr. Sulzberger recalls the experiments in the Zurich clinic, where it was found that culture mediums made from adult hair readily served as a medium for fungi, including *M. audouini*. Such observations support my contention that the secretions of the glands play a role in preventing infection rather than some substance possibly contained in the hairs themselves.

DR. MARION B. SULZBERGER: With regard to Dr. Kesten's suggestion of the likelihood of finding fungous infections in adults exposed to infected children: Even if that were the case, I am sure that persistent infection is rare in an adult. To be sure, occult and sporadic subclinical infections of adults may be more common than is supposed. I remember the experiments at Zurich mentioned by Dr. Peck. However, I found there that *M. audouini* grew very poorly on adult hair in vitro. The fungous inoculations on adult hairs formed the *fusca*, a spore regarded as indicative of poor and inhibited growth.

DR. HERMAN GOODMAN: An alkaline reaction is held to favor the microsporon infection of the scalp in children. Free acid sweating seems to produce improvement in the tinea. Adults show a  $p_H$  on the acid side. This served as a clue to the failure of many adults to become infected with the microsporon. Acid rinses were proposed and utilized for care of the scalp, the lemon rinse being a favorite.

It would be interesting if it were possible to determine the  $p_H$  balance of the scalp of preadolescent and postadolescent persons. The present modes of recording the  $p_H$  do not reflect the actual condition. Those available give only the  $p_H$  of the aqueous phase of an emulsion. No apparatus is yet available to give direct readings of the  $p_H$  of the oil side of an emulsion. The covering of the skin has the sweat-water phase and oil phase, representing the products of the sebaceous sacs. Perutz (Die Pharmakologie der Haut, in Jadassohn, J.: Handbuch der Haut- und Geschlechtskrankheiten, Berlin, Julius Springer 1932, vol. 5, pt. 1) cited some of the work in this field. Other pertinent references are: Beeler: J. Am. Pharm. A. (Practical Pharmacy Edition) 3:233, 1942 and Harry, R. G.: Hydrogen Ion Concentration in Therapeutic Bases, Brit. J. Dermat. 54:1, 1942.

Incidentally, will the presenters explain what was to be expected by offering hormone therapy? How, theoretically, would it affect the scalp? What safeguards were utilized to prevent undue influence of the hormone on the patient's normal sexual activities.

DR. HELEN O. CURTH: This woman also has alopecia areata. She still has spots on the occiput and shows loss of the eyebrows. I wonder whether this preceding arid accompanying disease of the scalp could not have caused some strange response to the infection with *M. audouini*.

DR. FRANK VERO: One of my colleagues informed me that he has used electrolysis with good results for the removal of residual hair which still showed fluorescence. With reference to the comments of Dr. Kesten and Dr. Sulzberger on examination with the Wood light, I see every afternoon in the clinic children sent from the board of health for whom a diagnosis of tinea capitis could not have been made clinically. There are no signs of any inflammatory changes, broken-off hair or bald spots, but examination with the Wood light shows fluorescence. I wonder whether the increase in the number of cases of tinea, said to be of epidemic proportions, is not due to discovery of more cases through application of the Wood light.

DR. SAMUEL M. PECK: It is no longer valid to doubt the ease of diagnosis of fungous infection of the hair by means of the Wood light. It has been shown in thousands of cases that an experienced observer can detect an infection of the

scalp with *M. audouini* in almost 100 per cent of cases provided the hair above the surface of the scalp is infected with the organism. The fluorescence is so specific that one could not fail to differentiate between fluorescence due to the organism and fluorescence due to something else.

DR. FRANK VERO: In answer to Dr. Peck, I should like to add that in the cases of tinea capitis I have seen at the department of mycology of the Vanderbilt Clinic in which there was no clinical evidence of infection examination showed a typical fluorescence of the hair, cultures yielded *M. audouini* and the hairs had to be epilated.

DR. MARION B. SULZBERGER: Dr. Vero means that many subclinical cases of true infection with *M. audouini* could not be recognized until the Wood light was introduced. He means that the correct diagnosis is being made more and more often since the advent of the Wood light and that one is now able for the first time to gain an accurate idea of the number of cases of subclinical infection with this fungus.

DR. EUGENE T. BERNSTEIN: L. M. Smith, of El Paso, Texas, inaugurated the idea of hastening puberty as a physiologic defense mechanism against the growth of *M. audouini*. Some of my colleagues have been obsessed with the idea of giving children such hormones as testosterone and estrogen. I think it is an intrusion into a child's being to give estrogens, for that changes the entire glandular apparatus.

DR. FREDERICK REISS: We assumed that injected estrogen could not reach the same level in the skin as that obtained with topical applications; so the substances were applied directly to the affected areas. We later changed to androgens. Under the treatment outlined, the infection was reduced to a certain extent. When the lesions did not completely disappear, thyroxin was given, on the assumption that there was a chance of changing the chemical state of the keratin and making it unsuitable for growth of *M. audouini*. It may have altered the progress of the disease, but the infection has not cleared up entirely.

Dr. Peck made an interesting point in his comment on the experiments at Zurich, and I believe the matter should be clarified. First of all, *M. audouini* affects the scalp first and only later involves the hair. In answer to Dr. Sulzberger, the fungicidal action of a substance isolated from the hair of adults, found by Rothman, takes place in vitro. It is generally recognized that results in vitro do not mean much when applied to conditions in vivo. Investigations have been made recently in the laboratory of Dr. G. M. Lewis in relation to the fungistatic effect of hormones on various kinds of fungi, and it is interesting to note how high the fungicidal effect of certain hormones is in vitro. The therapeutic relations, however, are in no way comparable to the laboratory results. Dr. Goodman brought out an interesting point concerning the  $p_H$  of the skin. Dr. Vamos investigated the problem of the  $p_H$  of the scalp of children and of adults. The  $p_H$  of children is much higher than that of adults. Applications of estrogens and androgens in a few of our cases of infection of the scalp with *M. audouini* shifted the  $p_H$  toward the acid side.

DR. MARGARET KLUMPP: One would expect that at least infection with *M. audouini* would be less tenacious and easier to eradicate in an adult, but in this case it has not been so. There were localized spots, and we performed epilation on these with roentgen irradiation; the infection seemed to be eradicated and all fluorescence disappeared for some time, only to reappear. Since then the infection has resisted all the remedies at hand. We have also tried manual epilation, but the infection is about the same as when the patient first came in, over a year ago.

## NEW ENGLAND DERMATOLOGICAL SOCIETY

Dr. Bernard Appel, M.D., President

G. Marshall Crawford, M.D., Secretary

Boston, Dec. 12, 1945

**Leukemia Cutis.** Presented by DR. JOHN G. DOWNING, Boston.

A 72 year old white man, T. E., is presented with a generalized dermatosis of seven months' duration. His eruption began as red pruritic papules on the face and head, soon spreading to the neck. Some time during the early stage of the disease, a cervical abscess developed, which was treated with penicillin. Later, the eruption spread more rapidly and became generalized.

This patient is a somewhat emaciated man who looks older than his years. There is a diffuse erythema of the skin with slight thickening and a fine scale. The forehead and neck reveal occasional large, indurated, dark red nodules, some as large as 1 cm. in diameter. The ears and the feet are moist with serous exudate and some crusting. The feet, ankles and legs exhibit an advanced degree of pitting edema.

A biopsy revealed changes suggestive of leukemia cutis. The hemoglobin was 13.0 Gm. The leukocytes of the blood numbered 20,000 per cubic millimeter. A differential blood smear showed 61 per cent polymorphonuclear leukocytes (including 11 band cells), 19 per cent lymphocytes, 16 per cent monocytes, 2 per cent myelocytes and 2 per cent metamyelocytes.

This man was given roentgen therapy by the spray technic of 700 r (in seven divided doses). The patient has also received radioactive phosphorus intravenously in a dosage of 15 millicuries. Several blood transfusions have been given. The response to therapy has been striking, and the point of presentation is the result of treatment with roentgen rays and radioactive phosphorus.

## DISCUSSION

DR. JOSEPH F. ROSS (by invitation): A new form of radiation therapy was made possible by the development of the cyclotron and the production of artificially radioactive isotopes. Of the artificially radioactive isotopes, radioactive phosphorus has been the most widely used. Radioactive phosphorus has proved to be a satisfactory substance for the treatment of chronic leukemia and also appears to be effective in the treatment of leukemia of the skin.

Radioactive phosphorus is given by intravenous injection, dissolved in isotonic solution of sodium chloride, and is metabolized by rapidly growing leukemic cells just as ordinary nonradioactive phosphorus would be. Owing to the increased rate of growth of these cells, they take up phosphorus more rapidly than normal nonleukemic cells, and the radioactive phosphorus is thus concentrated in the leukemic tissue. There it liberates its radiations (beta rays, or electrons) directly in the tissue, probably actually within the nuclei of the tumor cells. These cells are destroyed by the radiation, and the progress of the leukemia is retarded.

In patients with chronic myelogenous leukemia treated with radioactive phosphorus, the leukocyte count has been restored to normal levels, the character of the cells noted in the blood smear has returned almost to normal and the concentration of hemoglobin in the blood has risen to normal.

Two patients with leukemia of the skin have improved remarkably after treatment with radioactive phosphorus. Cutaneous lesions have practically disappeared, the blood picture has resumed closer to normal characteristics and there has been considerable subjective improvement, including disappearance of pruritus.

This treatment is still in the investigative stage, but certainly merits further trial. Treatment with radioactive phosphorus has some practical advantages over roentgen ray therapy. It can be given by physicians in the office without the necessity of calling in a radiologist. It does not produce radiation sickness, and since the radiation is delivered directly in the tissue adverse cutaneous reactions are not encountered. Unfortunately, radioactive phosphorus is still expensive. If, however, radioactive phosphorus, a by-product of the uranium "piles" used in the production of the atom bomb, could be made available for use of physicians, treatment with it would soon be much less costly than roentgen ray therapy.

**Sarcoma of Skin.** Presented by DR. AGNES ISRAELIAN, Boston.

E. A. is a 73 year old white woman of Swedish birth, on the front of whose left thigh a lesion developed nine years ago. This was a painless olive-sized swelling, which remained essentially unchanged until five years ago. Thereafter it gradually increased in size, and at some later date the patient discovered lumps in her left inguinal region. These nodes disappeared after three or four months, but the original lesion on the left thigh persisted, and several new ones have appeared near it within the last year. During the past two months, all lesions have become distinctly larger and have turned a reddish hue for the first time. Accompanying these developments, the inguinal lymphadenopathy has recurred. A nonproductive cough developed about a year ago and has persisted, accompanied with a loss of 20 or 30 pounds (9 to 13.6 Kg.) in weight. There has been no hemoptysis. The patient has had no known exposure to tuberculosis and denies symptoms which might suggest syphilis.

Physical examination reveals an elderly woman who appears to be in good health. The tongue is fissured, and the mouth is edentulous. The blood pressure is 140 systolic and 80 diastolic. The lungs are clear, and the heart seems normal. The abdomen is soft, and there is no demonstrable enlargement of the liver or spleen. Midway down the anteromedial aspect of the left thigh are five or six red firm nontender movable nodules imbedded in the skin. On the front of this thigh is a hand-sized area of deep induration without discoloration, to which the skin is attached. There is a chain of matted lymphadenopathy in the left inguinal region. There is bilateral enlargement of the submaxillary lymph nodes but no other detectable change in the lymph nodes. The terminal interphalangeal joints of all the fingers are somewhat enlarged.

Laboratory observations were as follows: Roentgenologic examination revealed nothing of note in the lungs except calcified lymph nodes at the left hilus. The bones of the hands, feet, pelvis, hip joints and thighs showed no abnormalities. Examination revealed the blood and urine to be normal. The protein elements of the blood were within normal limits. A biopsy specimen has been taken and the histologic section reveals sarcoma.

**DISCUSSION**

DR. FRANCIS P. McCARTHY: I examined the pathologic section. It showed a massive neoplastic cellular infiltrate of lymphoid type. The number of eosinophils was relatively low. There were occasional large multinucleated cells suggesting the Sternberg-Reed type. Except for the history, this suggests Hodgkin's disease. The clinical history, however, does not conform to Hodgkin's disease of the skin. I would suggest removal of a lymph node for further study. When lymph nodes are in groups or chains, it is more suggestive of Hodgkin's disease.

**Lupus Erythematosus.** Presented by DR. GEORGE SCHWARTZ, Malden, Mass.

membrane. Interspersed among the active ulcerations are numerous depressed scars of past lesions. These have deformed the tongue to a considerable extent and are distinct on the lower lip.

The Hinton and Kahn reactions of the blood were negative. The nonprotein nitrogen was 30 mg., the cholesterol 180 mg. and the sugar 90 mg. per hundred cubic centimeters of blood. The hemoglobin content of the blood was 72 per cent, erythrocytes numbered 4,900,000 and leukocytes 6,700, with a differential count of 60 per cent polymorphonuclear leukocytes and 40 per cent lymphocytes. Examination revealed that the urine was normal.

Treatment has included administration of E. R. Squibb & Sons' "basic formula" vitamin preparation (thiamine hydrochloride, riboflavin, nicotinamide and ascorbic acid) by mouth, thiamine hydrochloride, U. S. P., subcutaneously, sulfapyridine by mouth, six vaccinations against smallpox (no reaction), Castellani's paint and 1 to 1,000 merthiolate locally. One autoinoculation with fluid from one vesicle was without effect. After the first three inoculations against smallpox a decided improvement was noted. Castellani's paint seemed to relieve the discomfort considerably.

#### DISCUSSION

DR. FRANCIS P. McCARTHY: The term *periadenitis mucosa necrotica recursens* is to be found in diagnoses in textbooks on dermatology and stomatology, but I do not believe that I have ever seen a case for which I used that terminology. I think that the necrotic type of lesion which this girl presents is a variety of severe aphthous stomatitis. The lesions on the tongue are deep and painful. She has had most of the usual caustic topical applications applied to the lesions. As a result of this local therapy she has some scarring of the mucosa. There is one lesion on the lingual aspect of the lower lip which represents an early aphthous ulcer. Scarring of the lip is rare in aphthous stomatitis. There may be a familial type of chronic aphthous stomatitis. I have seen 3 children in the same family with the disease, and the mother also had it. If it is a disease caused by a virus the patient should improve with several doses of smallpox vaccine. I would continue the vitamin therapy and give her solution of potassium arsenite plus calcium and iron preparation and smallpox vaccine. Combining all these remedies, I believe that results in this type of case may be obtained.

DR. WILLIAM R. HILL JR.: I had a patient who was treated with penicillin locally, but without improvement.

NOTE (Aug. 26, 1947).—Between January and May 1946 the patient received seventeen weekly inoculations with smallpox vaccine. She was seen in October and reported that her mouth had been completely free from ulceration for six months, which was the longest period of freedom from ulceration she had ever experienced. She was seen again in March 1947 when she presented one small labial lesion which caused little discomfort. Four additional inoculations with smallpox vaccine were administered in March. Up to this time (August 1947) the patient has complained of occasional discomfort, but no blisters or ulceration.

**Mycosis Fungoides.** Presented by DR. FRANCIS P. McCARTHY, Boston.

**Syphilis on the Tongue, with Monilia Organisms.** Presented by DR. JOHN G. DOWNING, Boston.

A 73 year old white man, J. L., is shown with a complaint of sore burning tongue for the past nine months. This has at times been accompanied with burning of the entire mouth. The patient has been a tobacco chewer for years. The

Hinton reaction of the blood was positive in several tests nine months ago, but no treatment was administered because of the patient's age and the lack of other evidence.

The distal half of the tongue is distinctly shrunken and atrophic. The dorsum and sides reveal extensive geographic areas which are made up of grayish white leukoplakia. The latter is present also on the buccal mucous membrane. The remainder of the tongue is beefy red and smooth, except portions of the lateral aspects and the posterior dorsum, where there are small epithelial excrescences that suggest beginning degenerative changes.

Microscopic examination of scrapings of tissue from the tongue revealed clusters of sporelike bodies simulating organisms of the Monilia group. Cultures were on display which verified that impression. Roentgenographic examination revealed that the lungs were normal. There has been no treatment other than mild alkaline mouth washes, and the patient has improved symptomatically.

#### DISCUSSION

DR. FRANCIS P. McCARTHY: This man has typical interstitial syphilitic glossitis. There is atrophy with leukoplakia on a bright red smooth tongue with absence of papillae and involvement of the oral commissures. The patient has verrucous epithelioma of the left oral commissure. There is also a lesion on the dorsum of the tongue of the verrucous type. Monilia often is observed in the oral cavity, but has nothing to do with the fixed lesions on the tongue and oral mucosa.

DR. ETHEL M. ROCKWOOD: I saw the culture, but it did not suggest pathogenic Monilia albicans. There was insufficient penetration of the medium.

DR. JOHN G. DOWNING: We presented this case to illustrate the fact that the presence of Monilia in the mouth may be purely incidental. The organism in this instance was not *M. albicans*. It has been my contention that even if one does see *M. albicans*, it does not mean a great deal. If a pathogenic Monilia is observed on the skin, one should look elsewhere for a systemic disturbance, such as avitaminosis or tuberculosis.

DR. FRANCIS P. McCARTHY: Routine cultures of the oral cavity of students in the course in bacteriology at Tufts Medical School showed from 3 to 5 per cent of the cultures growing yeast organisms of the albicans type.

## Book Reviews

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**Atlas of Histopathology of the Skin.** By G. H. Percival, M.D.; A. M. Drennan, M.D., and T. C. Dodds, M.D. Price, \$16. Pp. 494, with 376 illustrations. Baltimore: Williams & Wilkins Company, 1947.

This book is a beautifully compiled atlas of histopathology of the skin, composed of 376 photomicrographs in color. They are the best colored reproductions using the Finley process that the reviewer has seen and the colors, even with special stains, are faithfully and accurately reproduced. The format of the book, including the arrangement of the text and legends, leaves nothing to be desired.

The authors state in the preface that they have attempted to portray in pictorial form the microscopic changes seen in the commoner diseases of the skin and, therefore, that the text matter has been severely limited to a brief explanation of the process illustrated. They have followed a clinical classification, grouping diseases according to the primary cutaneous change. This leads to a classification somewhat different from that seen in most textbooks on dermatology or in those on dermatohistopathology. The terminology employed is also different in many places from that used in standard textbooks previously mentioned, and because of this it would seem desirable in future editions to increase the glossary of terms, on the one hand, and add further synonyms, on the other. The reviewer would take exception, for example, to the inclusion under the term "psoriasiform carcinoma" of Queyrat's erythroplasia and Bowen's precancerous dermatosis and to the description of them as basal cell epithelioma, which they are not. Furthermore, the terms "superficial epitheliomatosis" or "erythematoid benign epithelioma" (Little) are more commonly employed than "psoriasiform epithelioma." There are a number of dogmatic statements in the text with which I doubt the majority of dermatologists would be in accord. Thus, on page 75 the authors state, in regard to lupus erythematosus: "The disease is generally regarded as having a definite connection with tuberculosis and has affinities with the sarcoids and granuloma annulare." For the most part, however, both the text and the legends under the illustrations are concise and well done. There is, however, a tendency to be too concise in certain descriptions; for example, in the two sentences describing mycosis fungoides there is no mention made of clumping of cells or pyknosis or karyorrhexis of individual cells, which are among the diagnostic features of this disease.

A few of the photomicrographs, although excellent reproductions, are of too low a magnification to bring out adequately the features of the disease in question or to fit with the descriptions in the legends under them. There is a relative lack of balance in regard to the number of photomicrographs of various diseases, especially some that are diagnostic histologically. Also, many illustrations are sometimes devoted to rare diseases; thus, for example, there is only one photomicrograph of lupus erythematosus but three of "orf" (*ecthyma contagiosum*), seven of cutaneous leishmaniasis and five of keratoderma blennorrhagicum. There are only four photomicrographs of psoriasis, not including any of so-called pustular psoriasis or recalcitrant pustular eruption; yet there are twenty-one photomicrographs of various types of "eczema," none of which present any special diagnostic histologic features. In the text on tuberculosis, one notes that such forms as inoculation tuberculosis, scrofuloderma and erythema induratum are not illustrated. Whereas leishmaniasis, which certainly is uncommon in northern countries, is included, there are no histologic pictures of lymphogranuloma venereum or

The rest of the text is written in concise diagrammatic style. Typical chapters are devoted to treatment for early syphilis, cardiovascular disease, prenatal infection, congenital syphilis and neurosyphilis. The information obtained from the results of careful study of all available reports is clearcut, specific and easy to understand. Less emphasis is placed on the use of penicillin in latent syphilis.

Moore has classified experts in syphilology into three groups. There is the middle group ". . . which takes the position that although present methods are in many respects unsatisfactory, new developments constantly occurring and new methods constantly introduced, it is nevertheless worth while to describe the best method of treatment now in use and to relate the attainable results." It is to this openminded group of physicians that this book will bring its maximum value. To all others who use penicillin for syphilis it is no less warmly recommended.

**Modern Dermatology and Syphilology.** By S. William Becker, M.D., and Maximilian E. Obermayer, M.D. Second edition. Price, \$18. Pp. 1017, with 461 illustrations in text and 37 full color plates. Philadelphia: J. B. Lippincott Company, 1947.

The second edition of this useful textbook is larger than its predecessor by one hundred and seventy pages. The material has been brought up to date, and the chapters on dermatologic therapy, pigmentary dermatoses and trophic and deficiency diseases have been amplified. A chapter on tropical diseases has been added. The importance of functional factors in etiology and therapy and the value of viewing dermatoses as processes rather than as morphologic entities are stressed.

Each chapter is introduced by a section on orientation, and the subject matter is presented in lecture rather than in encyclopedic form, which enhances its value to students and general practitioners of medicine.

The chapters on occupational and industrial dermatoses and eruptions due to drugs include useful charts and listings of substances which are important in the production of dermatoses.

The subject of syphilis is covered in two hundred and ten pages and includes chapters on the social aspects of the disease and the public efforts to combat it.

The text is printed on glazed paper in two columns per page. The illustrations are excellently reproduced. A short bibliography is included at the end of each chapter.

This edition should receive a hearty welcome from postgraduate students and practitioners of dermatology alike.



HOWARD FOX



## HOWARD FOX—A LEADER IN MEDICINE AND A GREAT DERMATOLOGIST

PAUL E. BECHET, M.D.

ELIZABETH, N. J.

There is to me an inexpressible charm in the lives of the good, brave learned men whose only objects have been and are to alleviate pain and to save life.—*G. A. Sala.*

DR. FOX, as editor of the ARCHIVES OF DERMATOLOGY AND SYPHILOLOGY for the past ten years, has, with his usual sense of fairness and justice and his inexhaustible capacity for work, carried on the onerous and time-consuming duties usually entailed by such a position. That he has been highly successful in this effort is only stating a fact known by the overwhelming majority of the devotees of the celebrated periodical which he nurtured for a decade and which on Jan. 1, 1948 will be seventy-eight years young. In that space of time not a single issue has been omitted. Its list of editors and the members of its various editorial boards read like a "Who's Who in American Dermatology," and in this constellate body Dr. Fox is a prominent member. His resignation causes his friends a feeling of discomfort and regret, but there are two mitigative factors: one, that Dr. Fox will have more leisure, and the other, that his mantle falls on the capable shoulders of Paul A. O'Leary, a member of the Editorial Board since 1944.

### THE MAN

Dr. Howard Fox was born on July 4, 1873, in London, England, where his parents were living temporarily. This event is recalled in his father's autobiography as follows: "The Fourth of July, 1873, we celebrated in a somewhat unusual manner. I cannot recall exactly what I did in honor of the day but remember with vivid distinctness the interesting circumstance that on that National holiday in a foreign land my wife presented me with a son and heir. Of course, he can never be President of the United States but there are still other fields of usefulness in which the United States Constitution does not hinder his efforts to achieve success." Apparently his father did not at that time foresee that dermatology would be that "field."

Dr. Howard Fox is a descendant of a notable family, among whose members may be mentioned William Coddington, John Sanford and

Peleg Sanford (three governors of Rhode Island) and Rev. James Noyes (one of the Founders of Yale College), William Chesebrough (Founder of Stonington) and Anne Hutchinson. His paternal grandfather, Norman Fox, was graduated from Union College in 1816, after having served in the War of 1812. For twelve years he was pastor of the Baptist Church at Ballston Spa, N. Y. Prior to his ordination he served as a judge of the Warren and Washington County courts and was a member of the State Legislature in 1819, 1820, 1826 and 1830. Dr. Howard Fox's father, George Henry Fox, was one of the most eminent of the early American pioneers in dermatology and the most prominent in New York. In his long span of life (1846-1937) he contributed greatly to the progress of dermatology. He was a founder (1876), president (1892) and honorary president (1926) of the American Dermatological Association on its fiftieth anniversary, receiving the gavel from the hands of his son, Howard Fox. He was president of the Medical Society of the County of New York (1891), president of the Medical Society of the State of New York (1894) and president four times of the New York Dermatological Society. At different times, between 1875 and 1907, Dr. George H. Fox served as professor of dermatology at the Women's Medical College of the New York Infirmary, Starling Medical College, Columbus, Ohio, Post-Graduate Medical School and Hospital, New York, and for twenty-six years at the College of Physicians and Surgeons, New York. This brilliant record, together with the capacity for friendship which Dr. George H. Fox always manifested, so beautifully expressed in his obituary by Dr. William Allen Pusey: "He was perhaps the friend of more American dermatologists than any other one of his generation," was probably the greatest psychic obstacle his son had to overcome in his early years. This would, of course, be accentuated by the fact that in the majority of instances a son in the same field as a famous father is apt to be only a reflection of the latter. There are, however, striking exceptions, and Howard Fox's brilliant career serves as an outstanding one.

Howard Fox received his primary education at the Columbia Grammar School, New York, graduating in 1890. In that same year he matriculated at Yale University, from which college he received the degree of Bachelor of Arts in 1894. He was awarded the degree of Doctor of Medicine from the College of Physicians and Surgeons of Columbia University, New York, in 1898. He interned at the J. Hood Wright Hospital, New York, from July 1, 1900 to July 1, 1902. Throughout the period spent in acquiring an education, both lay and medical, Fox studied assiduously, developing a capacity for work which

later in his career was to stand him in such good stead. His internship over, he decided to take up dermatology and left for Europe for graduate study. He spent eighteen months (1902-1904) under the tutelage of the leading men in that branch of medicine in Berlin and Vienna. On his return he immediately entered his father's services at the Vanderbilt Clinic and the New York Skin and Cancer Hospital, and about the same time he started his private practice in his father's office at the Sydenham Building (formerly the Madison Avenue Hotel), to which his father had recently moved. This building was the first professional office building in New York. It served as an office for father and son for many years, until the demolition of the building when Howard Fox with other physicians conceived the idea of a cooperatively owned medical office building, the first one in New York. Three houses were bought and completely remodeled. It was known as the Medical Chambers and was located at 114 East Fifty-Fourth Street. After years of successful management and occupation, it was sold, and a fine new building at 140 East Fifty-Fourth Street was constructed under the same plan of physician ownership and management.

By a strange coincidence, a mutual friendship arose between Dr. George H. Fox and me before I had met Howard Fox. This was in 1909-1911, and it well illustrates what I have so frequently repeated in my biographic writings referring to George H. Fox, namely, that he manifested an extraordinary degree of interest and cordiality for the young tyros of his specialty. Despite the fact that I was a dermatologic nonentity and he one of its stars, this friendship was not in the least altered. The same held true with Howard Fox, whom I met after my election to the Manhattan Dermatologic Society in 1912, where, for the first time, I had the opportunity to observe the clarity, objectiveness and accuracy of his dermatologic discussions. Later, my election to the New York Dermatological Society (1921), the American Dermatological Association (1929) and an appointment to Dr. Howard Fox's teaching staff at the School of Medicine at New York University (1925) gave me the unique chance to note through the passing of thirty-five years the blooming of his early knowledge of dermatology into the mature perfection of today. I have not infrequently noted that many dermatologists seem at their best when discussing some particular aspect of dermatology in which they might be particularly well versed, but it has been my impression that Howard Fox covered all the multitudinous facets of dermatology with equal clarity and minuteness. The fact that he is an expert on tropical dermatoses and has written much on the subject could not be ascertained in clinical discussions unless the patient presented a tropical cutaneous disease. He therefore always impressed me with his universal knowledge of dermatology, much in

the same sense that Sir Jonathan Hutchinson did in making himself, by means of his extraordinary ability, the greatest of the multispecialists, but with the notable difference that Fox remained entirely within the orbit of dermatology and Hutchinson did not.

As a man, Howard Fox has throughout the years always given evidence of his innate sense of integrity and fairness. In his multitudinous relationships with subordinates he has been gentle yet firm and, in the face of diagnostic disagreement with his opinion among his equals, extremely tolerant. He has a keen sense of humor, and I have both seen and heard him laugh most heartily at some of the jokes and airy badinage at the dinners of the New York Dermatological Society. At the Wednesday afternoon clinical conferences at New York University, over which he would preside, when the time came



Fig. 1.—Howard Fox, M.D., professor and head of the Department of Dermatology and Syphilology, New York University, College of Medicine, with his staff in 1937.

for him to make a diagnosis, it would be voiced in a manner entirely devoid of the usual "promulgation from the throne" style, so frequently observed in persons who are dermatologically weak. When Fox uses your first name in speaking to you, he likes you. It means something to him, as it properly should. Dr. Fox's capacity for work throughout his life has been phenomenal, as is well proved later in the recital by the record of his dermatologic achievements. A letter from an admirer in reference to his resignation as Editor of the *ARCHIVES OF DERMATOLOGY AND SYPHILIOLOGY* ends with the hope that he will have more time to enjoy the "pleasantries of life." He will, if the pleasantries of life mean further constructive work in dermatology, for Howard Fox's greatest hobby is and always will remain in that field.

Dr. Fox was always ready to correct the mistakes of those of us with a somewhat limited knowledge of Greek or Latin terminology when we were reading a clinical history or discussing a case. This was done in such a kindly manner and with such evident self satisfaction that it almost made it a pleasure to have made the mistake, for by so doing we greatly profited and at the same time afforded him the satisfaction of helping us.

Howard Fox occupies as high a position in dermatology as it is possible for any one to attain, yet he is as approachable as the least of us, despite the fact that there exists a certain aura of restraint which discourages familiarity. However, this is not in the least noticeable by his intimates. Fox's training in the amenities of social life and his inherited good taste are reflected in his dignified yet cordial bearing in all his human contacts, and his charm of conversation and good diction reflect his thorough education. He has throughout his career practiced medicine with such a high sense of duty and uprightness that he is naturally intolerant of the least deviation from medical ethics.

His faults are so very few, so very human and so much a part of all of us that they scarcely deserve that designation: he is fond of office; he likes praise; he is proud of his record and likes to see it in print, and he has a healthy hatred of any one who has seriously tried to harm him professionally. Not a single one of my readers (and this is also true of me) can conscientiously state that he himself does not possess each and every one of them.

#### THE DERMATOLOGIST

Dr. Howard Fox began his dermatologic career in his father's services at the Vanderbilt Clinic and the New York Skin and Cancer Hospital in 1904, after graduate dermatologic study for eighteen months in Berlin and Vienna. He had access to an enormous amount of clinical material in these two institutions for the next nine years and the advantage of his father's instruction, all of which proved a splendid foundation for his future dermatologic career. His ability was so early recognized that he was elected a member of the American Dermatological Association in 1908 and the New York Dermatological Society in 1909. He was elected vice president of the former in 1915-1916, president in 1925-1926 and historian in 1916 when this post was first established, a position he still holds. He also served as a member of the board of directors from 1938-1944. He served twice as president of the New York Dermatological Society, in 1915 and 1928. He was one of the early members of the Manhattan Dermatologic Society and was president in 1917 and 1933 and an honorary member since 1940. He was elected a Fellow of the New York Academy of Medicine in 1906 and

is a charter member of the Section of Dermatology and Syphilology, which he served as chairman in 1921-1923. In the American Medical Association he was secretary of its Section of Dermatology and Syphilology from 1913-1915 and chairman from 1915-1916. He was the first chairman appointed to the Scientific Exhibit of the Section of Dermatology and Syphilology in 1924 and a delegate from the Section in 1920, 1921, 1923, 1924 and 1925. He was awarded a certificate of merit for an exhibit of cultures of different fungi in 1927. He was the first president of the American Academy of Dermatology and Syphilology in 1938 and of the Association of Dermatosyphilologists of Greater New York in 1940-1941. The American Board of Dermatology and Syphilology was founded in 1932, and Fox was elected president, serving until 1945. He has been president of the Association of Syphilis Clinics since its formation in 1938. He had the honor of being the first chairman of the Section of Dermatology and Syphilology of the Medical Society of the State of New York, 1926-1928. In 1931, he was awarded the honorary degree of Doctor of Science at Rollins College, Winter Park, Florida.

Howard Fox was one of the vice presidents of the Deutsche Dermatologische Gesellschaft, Bonn, Germany, August 1929, vice president and secretary of the American delegation at the Eighth International Congress of Dermatology at Copenhagen, Denmark, in 1930 and one of the honorary presidents of the Ninth International Congress of Dermatology at Budapest, Hungary, 1935. He is an honorary member of the following local and foreign dermatologic societies: Austrian Dermatological Society (1936), Cuban Dermatological Society (1929), Hungarian Dermatological Society (1935), Manhattan Dermatologic Society (1940), New England Dermatological Society (first to be elected, 1920), Pittsburgh Dermatological Society (1921), Polish Association of Dermatology and Syphilology (1937), Royal Society of Medicine (Section on Dermatology) (1942), Society for Investigative Dermatology (1940), Sociedad de dermatologia y sifilografia (Argentina, 1942), Société Français de Dermatologie et de Syphiligraphie (1936), Société Française de Prophylaxie Sanitaire et Morale (1931) and Spanish Academy of Dermatology and Syphilology (1935).

He is also a corresponding member of the Danish Dermatological Society (1923) and the British Association of Dermatology and Syphilology (1927).

Dr. Fox has served the following hospitals as attending dermatologist: Red Cross Hospital (about 1910-1912), Harlem Hospital (1912-1925), New York Nursery and Child's Hospital (1926-1934, when the hospital closed), Lenox Hill Hospital (about 1915-1931), Willard Parker Hospital (1913-1941), Bellevue Hospital (1925-1938).

Riverside Hospital (1922-1939), United States Public Health Service, District 2 (1922-1946) and Veterans Hospital (1922-1947).

Dr. Fox is at present a consulting dermatologist at the following hospitals, arranged in chronologic order: Muhlenberg Hospital, Plainfield, N. J. (1912), Union Hospital (1912), King's Park State Hospital



Fig. 2.—Dr. Howard Fox after receiving the honorary degree of Doctor of Science from Dr. Hamilton Holt, president of Rollins College, Florida.

(1920), Lutheran Hospital (1922), United States Marine Hospital, Ellis Island (1922), United States Marine Hospital, Hudson Street (1922), United States Marine Hospital, Stapleton, Staten Island (1922), Manhattan Eye, Ear and Throat Hospital (1926), Knickerbocker Hospital (1928), Fifth Avenue Medical Center (1928), St. Vincent's Hospital.

Montclair, N. J. (1931), Lenox Hill Hospital (1931), Vassar Brothers Hospital, Poughkeepsie, N. Y. (1934), Beth Israel Hospital (1937), Bellevue Hospital (1938), Misericordia Hospital (1938), Riverside Hospital (1939), New York Post-Graduate Hospital (1941), Willard Parker Hospital (1941) and Metropolitan Hospital (1943).

#### THE TEACHER

Howard Fox received his first appointment as professor of dermatology at Dartmouth Medical School in 1913. This was followed by the professorship of dermatology and syphilology at the New York Poly-clinic Medical School and Hospital in 1922. He resigned in 1924, when he was offered the chair in dermatology and syphilology at the School of Medicine, New York University, in 1925, where for the succeeding thirteen years he had sufficient opportunities to use his rare gifts as an organizer and leader and, with large dermatologic wards in Bellevue Hospital and a large outpatient department, to demonstrate his ability as an expert clinician. One of his innovations was the Wednesday afternoon conference, at which time the most interesting and rarest dermatoses were exhibited to the students and the entire staff. Each case was discussed immediately after presentation, and the number was limited. Dr. Fox would seat himself directly in front of the patient, usually on a long and extremely hard bench, with the most prominent members of his staff next to him. After every one had inspected the lesions the discussion was usually started by the lesser tyros, rising in crescendo form to the higher-ups, which gave him rather the edge on us, for somebody would occasionally say something which would be of value in the diagnosis of a doubtful case. I enjoyed these conferences immensely, both from a dermatologic point of view and because of the opportunity to observe the ramifications of the dermatologic mind: the usual know-it-all, to be found in every clinic, who gives his discussion all the authority of an expert yet knows so little of dermatology; the egoist who believes that his diagnosis is correct and Dr. Fox all wrong and who will argue the matter *ad nauseam*, despite the fact that all the objective symptoms are against him; the foreign-educated gentleman who for years has served under the tutelage of this or that Herr Professor and who will discuss the most abstruse details of the dopa reaction, yet will muff the diagnosis of atypical pityriasis rosea, and the man who always prefaces his discussion with the statement that in Herr Doktor Yoghurst's clinic at the Universitate de Hokumstrasse he had observed a similar case or that in volume 799, page 72½ of the "Deutsche dermatographia," he saw a photograph of an identical case, all said to impress his hearers and throwing no light on the case. All these characters are part of any dermatologic clinic or meeting and were not in

the least restricted to the Wednesday afternoon conferences. The overwhelming majority of Fox's staff were regular fellows and good dermatologists. But I challenge any one with extensive clinical and teaching experience to state that my observations in reference to these pests are exaggerated. That even the best of us are not dermatologically omniscient is proved by the number of cases presented for diagnosis in the indexes of the ARCHIVES, but at least we admit our limitations and do not hide under the coats of our innocent superiors in order to make an impression on our audience.

Howard Fox, through the hardest kind of work, increased the prestige of the dermatologic division of the College of Bellevue Hospital and the clinic to such an extent that its reputation became national, and when he retired in 1938 he left a department which had greatly increased in size and importance, which was all he wished as a reward for the great amount of time and labor he had expended for thirteen years. He was, of course, elected professor emeritus by the University.

With his proverbial good diction, his appreciation for the importance of etymology, his unfailing courtesy and his knowledge of dermatology, he could not help being an excellent teacher. This was well demonstrated by the large attendance of his classes and the invariable enthusiastic applause at the end of his lectures. To the members of his staff he was understanding, just, easily accessible and a good listener. When it was necessary to reprimand any one he did it in such a way as never to give offense.

#### THE EDITOR

Howard Fox was elected to the Editorial Board of the ARCHIVES OF DERMATOLOGY AND SYPHILOLOGY in 1936, and only one year later became Editor-in-Chief. In succeeding Pusey he took on a herculean task, as the ARCHIVES under Pusey's direction had become the foremost dermatologic publication in the world. How well Fox succeeded in the ten years of his editorship is attested to by the increased popularity and scientific reputation of that periodical under his management. It has not only retained its position as the most important dermatologic journal, but has become the most useful source of dermatologic knowledge published today.

There is no magic to the present success of the ARCHIVES. It was not done with mirrors. The members of the board of trustees of the American Medical Association were canny in their selection of Fox, for he had all the prerequisites for editorial work; an inexhaustible capacity for work, courage to refuse undesirable articles, careful pruning of verbose contributions, elimination of presentations of cases of no interest and careful editing of articles. Besides these he had a thorough knowledge of etymology and literary style, and, last but not least, he personally perused each article submitted. Dr. Fox did more than this,

for according to his own testimony he read every word that was printed in the ARCHIVES except the advertisements. That this was a large order is proved by the fact that 3,003 articles were submitted for publication during his ten years as Editor, of which number 352 were rejected. How he has also found time to serve as collaborating editor of the *Acta Dermato-Venereologica*, Stockholm, Sweden, since 1929 and consulting editor of the *New York State Medical Journal* since 1939, with a membership on the editorial board of *Excerpta Medica*, Amsterdam, Netherlands, remains a mystery to me.

#### LEADER IN MEDICINE

Fox's nondermatologic medical activities can best be described in itemized fashion: American Medical Association—delegate to the Sixth Cuban National Medical Congress, 1924; delegate to the British Medical Association, Bath, England, 1925 (one of three delegates on the first occasion of sending delegates to that association); Medical Society of the County of New York—ten years of service as chairman of various committees, vice president 1936-1937, president 1938-1939 and trustee 1939-1941; Medical Society of the State of New York—delegate 1937-1941, and New York Academy of Medicine—member of the Committee of Sixty to raise funds for new buildings, member of the Committee on Public Health Relations (1936); member of the Committee on Admission (1936-1937) and chairman (1938). Fox is an honorary member of the New Hampshire State Medical Society, the Medical Society of Peru, the Plainfield Medical Society and the Medical and Surgical Society of São Paulo, Brazil.

#### THE SOLDIER

Howard Fox has accomplished so much in medicine that the magnitude of his work in that field tends to dwarf his splendid military record. He was commissioned a first lieutenant, Medical Officer's Reserve Corps, on Aug. 31, 1911 and attended training camps for medical officers at Gettysburg and Tobyhanna, Pa., and Plattsburg, N. Y., 1913-1916. He was elected vice president of the New York State Association of Medical Reserve Corps in 1916. During World War I he was in active service from April 14, 1917 to Aug. 7, 1919, filling the successive grades of captain, Medical Reserve Corps, April 2, 1917; major, Medical Reserve Corps, October 1, and lieutenant colonel, Medical Corps, Nov. 6, 1918. In the United States he was stationed at Fort Slocum for two months, at Fort Porter as adjutant of Hospital Unit "F" of Harlem Hospital for one month and at Camp Upton Base Hospital successively as adjutant, chief of genitourinary service, military instructor and liberty loan officer for fourteen months, including one month as camp

surgeon. On duty overseas he was commanding officer of troops on board the transport *La France*. On his arrival in France he was given the post of commanding officer of Base Hospital 136 at Vannes, Morbihan, France. He returned with his unit on the transport *Manchuria* and was the senior medical officer on board.



Fig. 3—Lieut. Col. Howard Fox, M.R.C., at Camp Upton, N. Y. He was later commanding officer, Base Hospital 136, Vannes, France

Fox was honorably discharged on Aug. 7, 1919 at Camp Upton and later was commissioned a colonel of the Medical Reserve, United States Army. He became the first commander of Caduceus Post 818 of the American Legion in 1920-1922 and again in 1938-1940.

In World War II he was appointed a consultant to the secretary of war in tropical diseases, giving lectures every two months for three

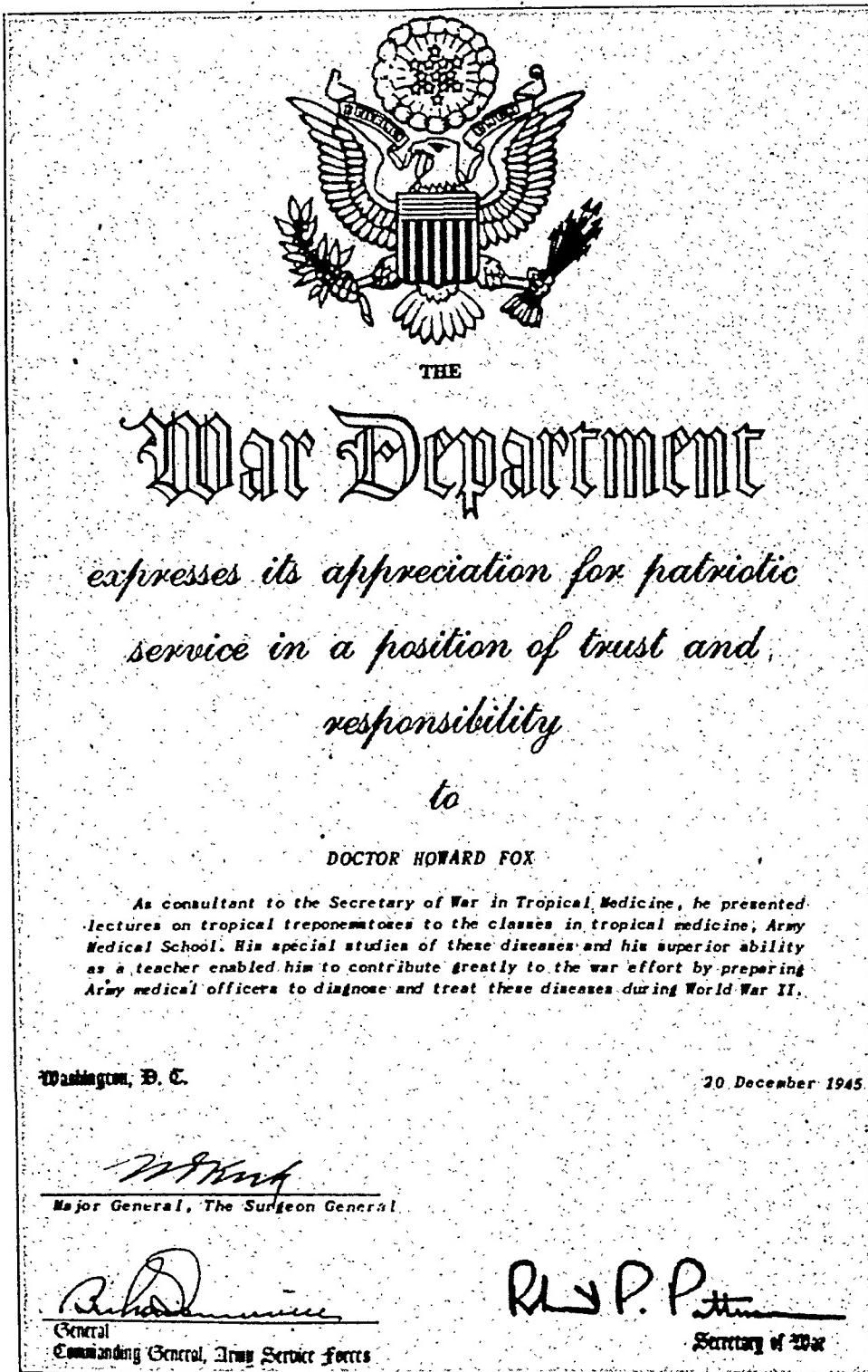


Fig. 4.—War Department certificate.

years at the Army Medical School in Washington, D. C. In his military career Fox followed a family tradition, as his great grandfather, Rev. Jehiel Fox, served in the Revolutionary War, his grandfather, Hon. Norman Fox, in the War of 1812, and his father, George H. Fox, and four uncles, Lieut. Col. William F. Fox, Major Charles J. Fox, Captain Norman Fox and Captain John J. Carter, in the Civil War. Captain Carter won the Congressional Medal of Honor. In World War I his only brother, Alanson G. Fox, served as a captain. In World War II, 43 cousins and nephews were in active service.

Howard Fox is a member of the following patriotic societies: Society of Colonial Wars, Sons of the Revolution, Military Society of War of 1812, Loyal Legion and American Legion.

#### EPILOGUE

Howard Fox is an outstanding example of the fact that man lives as he wills to live. As Sabouraud aptly expressed it in his farewell address at his scientific jubilee in 1929: "It is true, I have worked all my life. I have always considered myself as a tool, which I have put in service as best I could, but I must not glory in it; certain men are born workers, just as others are born lazy. If I have worked, it is because I never knew how to rest." I firmly believe that Fox became a human dynamo because of his devotion to dermatology and the desire to further the interests of our specialty, and besides he is fond of work. The innumerable honors he has received in recognition of his labors were amply deserved and not sought by him. In fact, my belief is that the multitudinous executive positions given him were offered with the knowledge that his appointment was the best that could be made by the organizations offering them, for they knew that he would do all he could to further their interests and serve them selflessly.

If Howard Fox had lived when knighthood was in flower, I would suggest the following motto for his coat of arms: *Labor Omnia Vincit*.

One of the great pleasures in writing of the more important achievements of one of the deans of American dermatology is the fact that this will serve as a prologue for some future historian, for, knowing Howard as well as I do, I am positive that in the many active years ahead of him the work he will produce will necessitate many additional pages to his biography. Men like him have a hearty hatred for what I have always considered an abominable triad, viz., the open hearth, carpet slippers and the easy chair. They are occasionally agreeable, but as a steady diet to be abhorred.

This chronicler lays down his pen with the hope that this modest attempt to depict the more important events in Howard Fox's life will please his innumerable friends.

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1364 North Avenue.

## HOWARD FOX

Reminiscences and an Appreciation

GEORGE M. MacKEE, M.D.  
NEW YORK

I MET Howard Fox in 1904 shortly after his return from eighteen months of graduate study in Berlin and Vienna. He was assisting his distinguished father in private practice in the old Sydenham Doctors' Building at Madison Avenue and Fifty-Eighth Street, in which my modest office was located. He was a member of the staff of the original Skin and Cancer Hospital, on his father's service, and an assistant in the Department of Dermatology, College of Physicians and Surgeons, Columbia University (Vanderbilt Clinic).

Our acquaintance quickly ripened into a friendship so strong that differences of opinion on important subjects actually strengthened mutual respect and trust. Occasionally, time proved my reasoning to be correct, but more often his was right.

I envied his education, his knowledge of dermatology and the German language, and I admired his enthusiasm, acumen, physical and mental alertness and intellectual versatility. He was and is intensely interested in music, literature, photography, the American Indian and other subjects. He was a natural linguist. We began the study of French at about the same time with the same teacher. He made more progress in one year than I made in two and with less effort.

About this time, 1906 to be exact, Wassermann, Neisser and Bruck announced the Wassermann test, based on previous research by Bordet, Gengou and others. Fox was not content to read, talk and write about complement, amoceptor and antigen. To satisfy his insatiable interest and curiosity it was necessary to establish a serologic laboratory. He was one of the first in this country to perform the original Wassermann test and to report results.

In the vernacular, Fox had many "firsts." He was one of the first dermatologists to study cutaneous diseases in the Negro and one of the first American dermatologists to make a study of tropical dermatoses. With Abramowitz, but independently, he was first to recognize dermatitis medicamentosa caused by phenolphthalein. He was first to use roentgen rays for geographic tongue. He was probably the first to employ this agent for molluscum contagiosum and syringoma. He presented the-

first case of pellagra before a medical society in New York. He was the first dermatologist to study and compare pinta in Columbia and Mexico. His opinion was that it was the same disease. He agreed with the Mexican commission that a fungus was not the cause. He was the first to identify the disease in Cuba and the Virgin Islands. He was the first chairman of the section on dermatology of the New York State Medical Society. He took an active part in the formation of the American Board of Dermatology and Syphilology and the American Academy



Fox (right) and MacKee, Canadian Rockies, June 1915.

of Dermatology and Syphilology and was the first president of each organization.

Fox has been an extensive traveler, partly for pleasure but mostly for study and investigation. He has visited every state of the Union, most of Canada, the West Indies, Central and South America and every country of Europe except Albania, Lithuania, Estonia and Latvia. Having made a number of trips with him, I can testify to his being a perfect traveling companion. In fact, my first vacation (1915) was a

trip of three weeks, arranged by him, through the Canadian Rockies to San Francisco to attend the Section on Dermatology and Syphilology of the American Medical Association, of which Fox was chairman, and, incidentally, to visit the World's Fair. We returned by way of National Glacier Park, after which we spent a day at the Mayo Clinic. Fox was ahead of me dermatologically, but athletically I thought that I could "show him a thing or two." But while in the mountains he did everything that I did, on foot or horseback, with enjoyment and without fatigue. A much later trip was to Dallas, Texas, to attend a meeting of the American Medical Association, then San Antonio, Texas, México, D. F., and Veracruz, Mexico, and Habana, Cuba. In México, D. F., by request of Prof. Jesus Gonzalez Uruena, Fox lectured to a class of students in French. My health was poor at the time and Fox took good care of me. However, I felt a trifle frustrated and humiliated by being compelled to sit still and watch him make a hard climb to the top of the Aztec temple, the pyramid to the sun.

Fox has a high degree of family pride. He created and edited the Fox family "news." He pestered his father, George Henry Fox, until the latter wrote his interesting autobiography "Reminiscences" (1926), of which I am the proud possessor of an autographed copy. Howard also encouraged his father, after the latter's retirement, to make genealogy a hobby and especially to trace the Fox family tree. The first American paternal ancestor was Thomas Fox of Concord, Mass., eight generations back. The first maternal American ancestor was Giles Gibbs of Windsor, Conn., also eight generations back. Among the noted ancestors were William Coddington, John and Peleg Sanford, all governors of Rhode Island; the Reverend James Noyes, one of the founders of Yale; William Chesebrough, founder of Stonington, Conn., and Edward Johnson, author of an early history of New England. The tree was traced to William the Conqueror and, collaterally, to George Washington, Peter Stuyvesant and Jonathan Trumbull. George Henry spent many years working on the Fox genealogy, which finally became voluminous. Fox is such a common name in all nationalities, religions and races that it is doubtful that Howard will ever begin where his father left off.

Many of Howard's ancestors were founders of Yale University or were Yale graduates, and as he is a Yale alumnus he naturally is a Yale "fan." He has good naturedly taken much "joshing" from intimate friends when Yale lost at football, baseball or rowing.

On the evening of April 20, 1938, a dinner was given for Howard Fox by his staff of sixty physicians. The occasion was his automatic 65 year age limit retirement from the New York University Medical School. It was my privilege to be a guest. The expressions of admiration and appreciation by members of the staff and their sorrow at losing their Chief were sincere and touching. He responded by thanking them

for their loyalty and efficiency. He promised to function as emeritus, consultant and adviser to the department and to continue actively in dermatology. He has kept the promise.

This dinner party caused me to reminisce about Howard Fox and to wonder how he had accomplished so much under discouraging conditions—what might be called hard luck. In the first place there was the unfortunate controversy between George Henry Fox and L. Duncan Bulkley which caused the former to resign from the Skin and Cancer Hospital. Howard and Fred Wise also resigned. I think that this was about 1908. A few years later, about 1913, John Addison Fordyce was appointed Professor of Dermatology and Syphilology, College of Physicians and Surgeons, Columbia University. This caused the automatic retirement of all members of the dermatologic staff (Vanderbilt Clinic) of which Howard Fox was a member. Unfortunately, Howard was not included in the reorganization. So Howard was without a clinic. During the next twelve years, while he was attending or consulting dermatologist to a number of hospitals and clinics, he had no clinic of his own. In spite of this handicap Fox presented a number of patients at each meeting of the three New York dermatologic societies, wrote many excellent articles and was active in local and national medical organizations.

For Howard Fox 1925 was an important year. It was in November of that year that he was appointed Professor of Dermatology and Syphilology, New York University College of Medicine. He was now the head of a good dermatologic service in a grade A university medical school which included a large free bed service in Bellevue Hospital. At last, Fox had the opportunity he had so long craved—the opportunity to prove his teaching, organizing and research abilities. Within a few years he had a large self-contained department with a staff of sixty physicians. He is a good forensic speaker and an excellent teacher. I had the opportunity to attend a few of his lectures to undergraduate students. The attention and applause he received were sincere and enthusiastic rather than simply polite. There were a number of popular innovations. One was, as often as possible, to introduce to his class dermatologic teachers from all over the world. I had the privilege of being present when William Allen Pusey, then the dean of American dermatology, was introduced and enthusiastically received. Another was to make Sunday rounds in Bellevue Hospital, to which students from other institutions were invited. This feature was greatly appreciated by my matriculates.

In 1937 Fox became Editor-in-Chief of the ARCHIVES, a position he held until 1947, a period of ten years. During his incumbency the ARCHIVES continued to grow in size and importance, in spite of a long major economic depression, a long global war and labor troubles. He gave editorial instructions to the secretaries, reporters or stenog-

raphers of each of the many dermatologic societies whose transactions were published in the ARCHIVES. This created a uniform literary style. He persuaded at least some of these societies to form a committee to edit their transactions and especially to delete cases unworthy of publication and irrelevant and lengthy discussions. He has used excellent judgment in accepting only articles of originality and merit, whether clinical or based on laboratory research. He has insisted on summation and conclusion. He has eliminated verbosity, repetitious contributions, unnecessary bibliographies and unessential and poor illustrations. Fox is an expert judge of illustrations, because photography has long been one of his hobbies. He has one of the largest collections of black and white photographs and lantern slides of cutaneous diseases in existence. He has never hesitated to call on members of the editorial board for an opinion relative to the merits of a submitted article.

Howard Fox has had almost every honor that an American dermatologist can receive. In this issue there is a formal biographic sketch by Paul Bechet which enumerates all these honors, positions and achievements, including army service.

I will enumerate what I consider Howard Fox's outstanding accomplishments: the building of a large first class dermatologic department for the training of undergraduate and graduate students, for research and for the care of the sick poor, the successful editing of the ARCHIVES over a period of ten years, his work at the head of the American Board of Dermatology and Syphilology for thirteen years, contributions to dermatologic literature—one hundred and fourteen articles in addition to a monograph on cutaneous diseases of children and chapters in a number of textbooks—twenty-eight months of service in the army (1917 to 1919) and his efforts in behalf of organized medicine.

Howard Fox has been retired as professor and director at New York University; he has resigned from the American Board of Dermatology, and now he has retired as Editor of the ARCHIVES. He was 74 years of age on July 4, 1947. He is one of the deans of American dermatology. His eyes and ears are perfect, and his health is excellent. His father lived to be over 90. We hope and expect that the son will do the same. In any event, the son will continue as emeritus, consultant and adviser to his former department and to various hospitals. He will continue his private practice and his activity in dermatologic societies and in medical organizations. In other words, he has many years of accomplishment ahead of him. As he recently said to me, while discussing festschriften of the past and future, "I am so glad that we are writing this sort of thing about one another instead of obituary sketches."

## COAL TAR IN DERMATOLOGY

An Improvement in Its Physical Properties Without Any  
Change in Its Therapeutic Action

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NEW YORK

MOST dermatologists will agree that crude coal tar is probably the most useful of topical remedies but, at the same time, one of the most difficult to handle pharmaceutically and one of the most disagreeable, both from an esthetic and cosmetic standpoint.<sup>1</sup> Ever since its use in the treatment of cutaneous disease was first specifically reported by Fischel<sup>2</sup> in 1894 it has been subject to criticism on these accounts, and in consequence has been offered to physicians as a tincture, liquor, filtrate, distillate and fractionate.<sup>3</sup> Few of these have proved very useful, and none of them has exhibited therapeutic activity equal to that of total crude coal tar. In every purified product some important ingredient seems to be lacking.

It is not the purpose of this article to discuss the various methods of manufacture of crude tar. Suffice it to say that its composition is dependent primarily on the type of coal, coke, petroleum, shale, lignite or other substance used as a source. Other factors involved are the type of retort used, the temperature of distillation, the rate at which that temperature is developed, the amount of superheated steam used and from what level in the tank the tar is obtained. It is obvious that there are tremendous possibilities for variation in the chemical and physical properties of crude tars available from the many drug outlets.

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From the Department of Dermatology and Syphilology, New York University College of Medicine and the Third (New York University) Medical Division, Bellevue Hospital.

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The objectionable physical and chemical features of coal tar have been instrumental in precluding its use in the complete and full range of its therapeutic capabilities. Not only its color, odor, chemistry and varying consistency and activity have been found objectionable, but its lack of pharmaceutic flexibility and its poor solubility have greatly limited its use. Without doubt, if these shortcomings could be dispelled it would have a much broader application than it does at present. Some of the important objectionable features of crude tar, other than its color and odor, are briefly outlined.

1. It is immiscible with water. This offers considerable difficulty when coal tar is prescribed for baths, apart from the problem of washing the sticky residue from the tub. It also limits its incorporation in various shake lotions, solutions, jellies and other hydrous vehicles.

2. There is extreme difficulty in the removal of some of the constituents of crude tar from the skin, and permanent stain is left on clothing and linens. In addition, many dermatologists are of the opinion that crude tar pastes are actually contraindicated on the scalp and other hirsute areas. White<sup>4</sup> recommended clipping the hair of the occiput, vulvar and perineal regions before application of crude coal tar paste to these areas.

3. Many pharmacists are incapable of compounding satisfactory coal tar preparations. This may not be necessarily due to lack of ability but to lack of proper equipment and to unavoidable variations in the tars used.

White laid particular emphasis on the necessity for a smooth homogeneous paste, claiming that improperly compounded pastes were frequently irritating. The proper method of combining the four ingredients usually used in pastes, namely, crude coal tar, zinc oxide, starch and petrolatum, has been the subject of constant controversy. If the final product is black it is an indication that the zinc oxide has been well triturated with the tar, the starch with the petrolatum and both separate mixtures then thoroughly incorporated with each other. This method assures a smooth homogeneous paste, with no grit or particles of pitch.

The greenish black preparation which results when the ingredients are not treated in exactly this manner is usually lumpy in consistency and gritty, with visible free particles of pitch and carbon. This second preparation is certainly not as acceptable therapeutically as the first. However, when the greenish black product is carefully and painstakingly compounded—when thorough and intensive milling yields a smooth

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4. White, C. J.: Crude Coal Tar in Dermatology, Arch. Dermat. & Syph. 4:796 (Dec.) 1921.

uniform product, free of particles of grit—it may be as effective as the jet black one. Unfortunately, in this method of manufacture special homogenizers and other pharmaceutical equipment are required.

The search for an answer to these therapeutic and pharmaceutic problems has been continuous. The solution appears to reside not in the removal of any of the objectionable components of tar but in a method of manufacture which would result in a crude coal tar with the following attributes: (1) complete miscibility and solubility in water, (2) retention of all the therapeutic activity of coal tar (this requirement interdicts any change in color by removal of any constituent, since this has been shown to impair its medicinal value), (3) fairly uniform chemical composition and (4) improvement in its physical properties so as to facilitate its use and increase its range of medicinal application.

There is now available a low temperature retort crude coal tar which appears to conform to the standards outlined. The qualities of crude tar which are obnoxious have been almost completely eliminated, not by removal but by rendering them more acceptable pharmaceutically and esthetically.

This tar can be easily incorporated in ointments, pastes, creams, and suppositories, petrolatum and wool fat, and on being mixed with water, glycerin, alcohol, collodion, tincture of benzoin, liniment of soft soap, water-soluble jellies, calamine lotion and many other liquids and suspensions it is readily miscible and compatible.

The accompanying table is a summary of clinical observations in a representative group of 36 patients for whom this water-soluble crude coal tar was prescribed.<sup>5</sup>

The following points are indicative of the potential pharmaceutic and medicinal advantages of this crude coal tar.

1. Manufacture of this tar with definite specifications and conditions consistent with the production of a medicinally satisfactory product provides a more uniform and constant source of tar which is comparatively unvarying in physical properties and chemical composition.

2. The miscibility of this tar renders compound ointment of coal tar (White's ointment) and its modifications smooth, uniform, homogeneous, soft and nongritty, and they are applied and removed with minimal effort and irritation. Pastes and ointments prepared with this

5. This crude coal tar ("zetar") was supplied to the dermatologic wards at Bellevue Hospital by the Dermik Pharmacal Company, Brooklyn. For the past eighteen months it has replaced ordinary crude coal tar in all instances in which tar therapy was indicated.

tar, because of the hydrophilic nature of the tar, apparently do not impede exudation, sweating and evaporation from the cutaneous surface. This may explain why acne due to tar and pustular folliculitis

*Summary in Thirty-Six Cases in Which Treatment Was with a Crude Coal Tar Product ("Zetar")*

Patient	Age	Sex	Race	Diagnosis	Involvement	Medication	Results
T. S.	61	M	W	Exfoliative dermatitis	Generalized	1 oz.* of tar to bath	VG†
E. R.	56	M	W	Disseminate neurodermatitis	Generalized	½ oz.‡ of tar to bath	VG
R. M.	21	F.	W	Infectious eczematoid dermatitis	Face, scalp, legs	1 oz. of tar to bath	F§
R. H.	28	F	N	Contact dermatitis	Face, hands, ears	5% tar ointment	GI
S. N.	62	M	W	Hypostatic dermatitis	Both legs	5% tar ointment	G
J. C.	54	M	W	Contact dermatitis	Both legs	5% tar ointment	VG
W. H.	53	M	N	Contact dermatitis	Arms, thighs, trunk	5% tar ointment	G
J. M.	53	M	W	Dermatophytosis	Feet, hands	5% tar ointment	G
J. F.	55	M	W	Hypostatic dermatitis	Back, thighs, legs	10% tar ointment	G
I. D.	42	F	W	Contact dermatitis	Generalized	1 oz. of tar to bath	VG
T. K.	80	F	W	Hypostatic dermatitis	Legs, thighs	10% tar ointment	VG
C. J.	22	F	W	Chronic contact dermatitis	Arms, face, neck	5% tar ointment	G
B. M.	33	F	W	Infectious eczematoid dermatitis	Legs, thighs, back	5% tar ointment	G
Y. K.	53	F	W	Infectious eczematoid dermatitis	Face, scalp, buttocks	10% tar in water	VG
D. C.	42	M	W	Infectious eczematoid dermatitis	Chest, arms, groin	5% tar ointment	G
J. M.	61	M	W	Contact dermatitis	Legs, arms, thighs	5% tar ointment	F
M. G.	21	F	W	Seborrheic dermatitis	Scalp	10% tar, cotton-seed oil	VG
S. D.	22	F	W	Chronic contact dermatitis	Face	Tar (full strength)	G
J. P.	39	M	W	Psoriasis	Generalized	5% tar ointment	G
E. A.	48	M	W	Hypostatic dermatitis	Legs, feet	5% tar ointment	VG
M. S.	75	M	W	Hypostatic dermatitis	Legs, feet	10% tar ointment	G
F. S.	58	M	W	Psoriasis	Generalized	5% tar ointment	G
M. B.	49	F	W	Exfoliative dermatitis	Generalized	2 oz.¶ tar to bath	VG
M. S.	21	F	W	Atopic eczema	Arms, neck, chest	5% tar ointment	G
E. S.	20	F	N	Infectious eczematoid dermatitis	Ears, arms, legs	5% tar in collodion	G
M. F.	46	F	W	Varicose ulcer	Legs, feet	5% tar ointment	F
M. L.	61	M	W	Psoriasis	Generalized	5% tar ointment	G
B. J.	58	M	W	Hypostatic dermatitis	Left leg	5% tar, collodion	G
F. H.	57	M	W	Atopic eczema	Legs, feet	5% tar ointment	G
C. S.	39	M	W	Contact dermatitis	Hands, feet	5% tar ointment	VG
J. R.	50	M	W	Chronic contact dermatitis	Arms, legs	20% tar in water	G
L. L.	31	F	W	Contact dermatitis	Scalp, ears	20% tar in water	G
J. B.	22	M	N	Seborrheic dermatitis	Scalp, ears	20% tar, cotton-seed oil	VG
F. D.	55	M	N	Chronic contact dermatitis	Arms, legs, chest	20% tar in water	G
L. B.	34	F	N	Exfoliative dermatitis	Generalized	20% tar, cotton-seed oil	G
E. R.	46	F	W	Infectious eczematoid dermatitis	Abdomen, back, thighs	10% tar, cholesterol base	VG

\* 28.347 Gm.

† VG is very good or complete improvement.

‡ 14.173 Gm.

§ F is fair or partial improvement.

¶ G is good or almost complete improvement.

|| 56.694 Gm.

are seldom seen when treatment is with this tar. In contrast to ordinary crude tar, no special processes, such as homogenization and milling, are necessary to attain a satisfactory paste or ointment. In addition, linens

and clothing are not permanently discolored. The usual washing with soap and water removes this hydrophilic tar from linens even when the base is a nonsaponifiable hydrocarbon.

3. The application of ointments, pastes, lotions and the like to multiple lesions in generalized and universal dermatoses is often inconvenient, messy, expensive and time consuming. When low concentrations of tar are desired for medicating extensive areas,  $\frac{1}{2}$  ounce (14.173 Gm.) of this tar added to a lukewarm bath will produce a nonstaining colloidal solution without any of the usual disadvantages. This is an effective and acceptable procedure, especially before retiring for the night, when, because of its antipruritic action, it is conducive to restful sleep.<sup>6</sup>

4. Subsequent to Goeckerman's<sup>7</sup> preliminary report, Fleischauer<sup>8</sup> in 1930 showed that the photosensitizing effect of coal tar is even greater when the tar has been completely removed from the skin prior to radiation with ultraviolet light than when a thin layer is allowed to remain, as recommended by Goeckerman. The reaction occurs even after the tar has been applied for only fifteen minutes and the area is irradiated as long as seventy-two hours after its removal.

The Goeckerman treatment may be pursued by the patient with much greater ease by applying the pure tar with a brush fifteen to thirty minutes each morning and then bathing, thus removing the tar completely and easily; or it may be readily removed with a damp cloth. Ultraviolet rays may be administered later in the day at the physician's office.

Unlike ordinary coal tar, this tar can be used on hairy areas and can be completely removed with water alone. This is a definite advantage, since ordinary tar is removable only with great difficulty from hair, even by means of harsh detergents and solvents.

5. Frequently psoriasis and herpetiform eczema occur in widely scattered patches. Treatment may consist of "spot touching" with 10 per cent of this tar in collodion. When it dries, it leaves a thin smooth black film which does not rub off or stain clothing and linen. However, it is easily removable from the skin with a damp washcloth or water alone. No soap or other detergent is necessary.

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**SUMMARY**

A low temperature retort crude coal tar is presented, which is processed to endow it with many advantageous features, most significant of which are: complete miscibility with water to form a colloidal solution; miscibility with collodion, rendering this substance easily removable from the skin with plain water, and miscibility with fixed oils, glycerin, pastes and fatty bases, which facilitates removal of these substances from the skin and clothing. These features have been incorporated without interference with the chemical composition, pharmacologic or therapeutic attributes of crude coal tar.

104 East Fortieth Street.

## ACNE ROSACEA

A Vitamin B Complex Deficiency

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ACNE rosacea belongs to that group of cutaneous diseases which have been attributed to many causes, as often is the case in a disease of obscure causation. The following have been advanced as causal factors: alcoholism, pelvic congestion, menopausal flushing, vasomotor disturbances of the male climacteric, gastrointestinal disorders (some claim 90 per cent of cases due to this factor), focal infection, obesity, organic disturbances, vasomotor neuroses, exposure to the elements and pastries and pies in the diet.

It is my belief that most, if not all, cases of rosacea are due to a vitamin B complex deficiency and that all the causes heretofore mentioned may be exciting or underlying factors, but are not immediately causal.

The term "brandy face," which both laymen and dermatologists often have used, we know today to be misleading. Although it is true that alcoholism is frequently a predisposing factor, I believe it to be so only indirectly. Frequently alcoholic persons, particularly when on a "spree" neglect to eat, sometimes to a point of starvation. Consequently they must suffer from a vitamin deficiency. This was well demonstrated during the days of prohibition, when Dr. Maloney and I<sup>1</sup> collected 21 cases of alcoholic pellagra among derelicts brought into Bellevue Hospital during one summer. They all gave the same story of having been on a drinking spree for several weeks and of having consumed only one bowl of soup each day. Supporting this theory of vitamin B complex deficiency are the observations in a case of Plummer-Vinson syndrome with associated acne rosacea in a woman 35 years of age, who was the mother of two and who never had more than an occasional drink of wine. She came to our clinic for treatment for a burning sensation of the tongue and dysphagia of two years' duration. She also presented acne rosacea with papules and telangiectasia over the nose, adjacent part of the cheeks and chin. This, incidentally, was of no concern to her, her interest was only in the burning sensation of her tongue. Examination of the blood

1. Maloney, E.: and Tulipan, L.: Alcoholic Pseudo Pellagra, New York State J. Med. 29:1063-1064 (Sept. 1) 1929.

revealed hypochromic microcytic anemia, and gastric analysis showed normal acidity. Since peripheral vasodilatation has been described as a manifestation of subvitaminosis B, I believe that the telangiectasia in this case is thus explained. Additional support of this theory was given by her immediate response to treatment. She was placed on a diet rich in vitamins and was given brewers' yeast tablets and ferric ammonium citrate for her anemia. Within two weeks the glossitis and rosacea cleared completely. Several months later she had a recurrence because of gradual regression to her old dietary regimen. Repetition of the same treatment again cleared up the glossitis and rosacea. The results in this case altered my therapeutic approach to succeeding cases. I placed far more stress on a high intake of vitamin B complex, sometimes to the complete exclusion of other systemic and local treatment, and my results were superior to any that I had achieved before.

Chana and Verdaguer<sup>2</sup> stated that they obtained excellent results with riboflavin alone. My own experience indicated that better results were obtained with the entire vitamin B complex, such as is contained in brewers' yeast. I believe that in all cases of acne rosacea attributed to gastrointestinal disturbances vitamin deficiency is the main factor. Gastroenterologists have stated that it is possible for persons who have a well balanced diet to have vitamin deficiency because of faulty assimilation. I have observed this to be true in several cases of rosacea which I studied, and vitamin therapy was proved to be indicated. Achlorhydria was present in only 30 per cent of the cases in my experience. In fact, some cases of indisputable rosacea were associated with hyperacidity.

My series of 96 patients over a period of eight years presented the various rosaceous manifestations, such as erythema, telangiectasia, papules, pustules and hypertrophy. There was also 1 patient with rhinophyma and 1 with corneal ulceration producing partial blindness. In those patients in whom the blood and gastric secretions were studied, hypochromic microcytic anemia was seen in 10 per cent and anacidity in 30 per cent as previously stated.

I found the following to be of little or no therapeutic value: the avoidance of hot food and drinks, tea, coffee and chocolate, alcoholic beverages, spices, hot and stuffy rooms, treatment with ergot, thyroid or dilute hydrochloric acid (for control, some patients received dilute hydrochloric acid; no advantage was demonstrated). Routinely I prescribed a diet rich in vitamins, supplemented with 6 brewers' yeast tablets and daily 15 grains (0.97 Gm.) of iron and ammonium citrates or ferrous sulfate.

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2. Chana, P., and Verdaguer, J.: Arriboflavinosis, Rev. argent. dermatosif. 26:51-54, 1942.

Patients should be warned not to use iodides (including iodized salt) or bromides. For patients who exhibited pustules or cutaneous hypertrophy I also used the following ointment:

	Gm. or Cc.
Red oxide of mercury.....	0.075
Precipitated sulfur .....	1.5
Salicylic acid .....	1.0
"Quinolor compound ointment" <sup>3</sup> .....	2.0
"Aquaphor" in sufficient quantity to make..	30.0

I have observed that roentgen therapy is of value in only a few selected cases. It has been my experience that patients with rosacea frequently are decidedly sensitive to both ultraviolet and roentgen rays. I have observed erythema following only one exposure of 75 r in many patients.

#### SUMMARY AND CONCLUSIONS

Although avitaminosis has been mentioned as one of the possible causes of acne rosacea, it was never considered as the primary cause in most or possibly all cases. Studies of cases in which large doses of vitamin B complex were used support my contention that vitamin B deficiency is the primary cause in most or possibly all cases. I believe that all causative factors previously mentioned in the literature are only underlying or contributing and not primary. Achlorhydria was observed in only 30 per cent of the cases in my experience and dilute hydrochloric acid as a therapeutic adjunct was found to be not necessary. In many cases of rosacea there is a decided sensitivity to both roentgen and ultraviolet rays. Roentgen ray therapy is of limited value.

50 Park Avenue.

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3. This product (E. R. Squibb & Sons) contains 10 per cent benzoyl peroxide and 0.5 per cent "Quinolor" (a mixture of three chlorine derivatives of 8-hydroxy-quinoline) in a base of equal parts of petrolatum and wool fat.

## OCCUPATIONAL PIGMENTARY CHANGES IN THE SKIN

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JEGHERS<sup>1</sup> stated that according to Edwards and Duntley the normal color of the skin is due to (1) the light reflection properties of its structure plus the cutaneous pigments, (2) melanin, (3) melanoid, (4) carotene and (5) hemoglobin and oxyhemoglobin.

Occupational exposures which produce disturbances in these five color factors of the skin may result in occupational pigmentary changes. Occupational pigmentation of the skin may consist of (1) an excess of melanin and melanoid, (2) deposits of metallic substances in the skin (tattooing) and (3) dyeing of the skin either from external application of the dye or deposition of the dye in the skin after ingestion.

### OCCUPATIONAL MELANODERMA

The occupational causes of excessive formation of pigment in the skin are (1) excessive exposure to sunlight or actinic rays, (2) exposure to coal tar (the heavy coal tar distillates and coal tar pitch), (3) exposure to crude petroleum and residues of petroleum distillation and "cracking" and (4) exposure to asphalt.

The last three substances are photosensitizers, and workers exposed to them either in the form of dusts, vapors or fumes complain of photosensitization, especially in bright sunlight. If the exposure is sufficiently often, in most of the workers there develops a peculiar deep yellowish brown discoloration of the exposed skin, different from the "tan" due to exposure to sunlight or actinic rays. The pigmentation of the exposed skin resulting from exposure to coal tar (its heavy distillates and pitch) is due partly to an excessive amount of melanin in the epithelial layer and partly to an actual dyeing or discolored skin by the coal tar itself.

In some workers, especially those with fair skin, melanoderma fails to develop, and the photosensitization dermatitis may become so severe that they must leave their occupation. A few workers with fair

1. Jeghers, H.: Pigmentation of the Skin, New England J. Med. 231:88-100 (July 20) 1944.

skins have experienced an urticarial type of eruption after exposure to coal tar pitch and sunlight.<sup>2</sup>

Apparently melanoderma is a protective mechanism against photosensitization, but that pigment alone does not prevent photosensitization is shown by the fact that Negroes exposed to coal tar pitch complain of burning of the skin when exposed to bright sunlight.

After exposure to coal tar ceases the pigmentation fades and entirely disappears in about a year, but the photosensitization may persist for a longer period.

Some of the fluorescent coal tar dyes, especially the derivatives of fluorescein, are known photosensitizers. Their use in lipstick and nail lacquers has been reported<sup>3</sup> as a cause of cheilitis and dermatitis, but hyperpigmentation independent of that which may follow an inflammatory process has not been reported.

Those in the principal occupations in which coal tar and petroleum cause photosensitization and melanosis are: (1) workers in coal tar distillation plants who come in contact with the heavy coal tar distillates and pitch, (2) workers making conduits by impregnating paper tubing and roofing by impregnating paper sheets with coal tar pitch or heavy coal tar distillates, (3) workers using paint containing heavy coal tar distillates or pitch, as in rust proofing iron piping, (4) workers in wood preserving plants where heavy coal tar distillates are used to impregnate railroad ties, telegraph poles, pier supports and the like, (5) road makers, especially those using pitch and asphalt, (6) briquet makers who use coal tar pitch to make fuel briquets from coal dust, (7) petroleum refinery workers, especially those cleaning stills and "cracking" equipment, and (8) workers in oil fields, especially those who drill, repair and service old wells.

The prevention of melanosis among workers with coal tar, petroleum and their photosensitizing derivatives consists in (1) preventing contact of the skin with the substances by installing either totally enclosed process or local exhaust hoods to draw away from the worker mists, fumes, vapors and dusts, (2) applying to the face, neck, hands and other exposed parts a protective ointment which is opaque to light and which also serves to keep the chemicals off the skin<sup>4</sup> and (3) supplying adequate facilities for frequent washing of the exposed parts.

2. Foerster, H. R., and Schwartz, L.: Occupational Melanosis from Pitch, Arch. Dermat. & Syph. 39:55-68 (June) 1939.

3. Schwartz, L., and Peck, S. M.: Cosmetics and Dermatitis, New York, Paul B. Hoeber, Inc., 1946.

4. One formula for such an ointment is: shellac 13, isopropyl alcohol 41, titanium dioxide 12, sodium perborate 12, iron oxide 0.5, linseed oil 4, talcum 9.5, "carbitol" 3 and isobutyl paramino benzoate 5.

## ACTINIC MELANOSIS

Melanosis develops also in most workers who are exposed to excessive sunlight. The hyperpigmentation (tan) is said to be due partly to the formation of extra melanin in the basal layers and partly to thickening of the stratum corneum.

The melanin may be deposited unevenly and be concentrated in small spots forming freckles (ephelides). Freckles are more likely to occur in blonde persons, in whom they often persist even after excessive exposure to sunlight is discontinued.

After excessive exposure to actinic rays ceases, the pigmentation fades and in a few months it is all gone. Some blondes do not "tan" and may suffer from severe "sunburn" after each excessive exposure, and after a time in many of them keratoses and epitheliomas develop.

Farmers, sailors, road makers, field workers and others who are exposed to excessive amounts of sunlight may be affected by occupational natural actinic ray hyperpigmentation. Exposure to actinic rays from therapeutic lamps, as in the case of technicians, and electric arcs as in the case of electric welders, may result in occupational melanotic cutaneous changes.

OCCUPATIONAL PHOTOSENSITIZATION AND MELANOSIS  
FROM PLANTS

Farmers, florists, horticulturalists and field workers may become photosensitized by contact with or ingestion of certain plants, and as a result of the photosensitivity protective melanosis develops. Animals, especially those that are white, become photosensitized from eating certain plants. The accompanying table lists the known photosensitizing plants and the method of their action.<sup>5</sup>

Recurrent attacks of dermatitis and chronic dermatitis may also result in hyperpigmentation. Continued friction or scratching of the lesions may result in melanosis. Occupations which entail prolonged standing, such as those of a policeman, letter carrier and waitress, may cause stasis of blood in the legs and subsequent pigmentation due to the deposit of blood pigment (hemosiderin) in the skin. Chronic ulcers of the leg, especially in those past middle life, are usually surrounded by areas of hyperpigmentation due to the deposit of hemosiderin in the chromatophores. Workers exposed for long periods to heat from open flames, such as welders, glass workers, foundry workers, stokers and blast furnace workers, may experience reticulated

5. Muenscher W. C.: *Poisonous Plants of the United States*, New York, The Macmillan Company, 1939.

## Photosensitizing Plants

Botanical Name	Family	Common Name	Mode of Action	Affects	Comment
<i>Agave lechuguilla</i>	Amyllidaceae	Lechuguilla	Ingestion	Cattle	
<i>Andropogon citratus</i>	Gramineae	Lemon grass	Contact*	Man	
<i>Andropogon nardus</i>	Gramineae	Lemon grass	Contact	Man	
<i>Andropogon schoenanthus</i>	Gramineae	Lemon grass	Contact	Man	
<i>Citrus aurantium</i>	Rutaceae	Bergamot	Contact	Man	Berlocque dermatitis
<i>Citrus medica acidia</i>	Rutaceae	Lime	Contact	Man	
<i>Dictamnus albus</i>	Rutaceae	Gas plant	Contact	Man	
<i>Daucus carota</i>	Umbelliferae	Wild carrot	Contact	Man	
<i>Fagopyrum esculentum</i>	Polygonaceae	Buckwheat	Ingestion	Man	Action is due to a fluorescent ingredient or to a parasitic fungus
<i>Fagopyrum tataricum</i>	Polygonaceae	India buckwheat	Ingestion	Man	
<i>Ficus carica</i>	Moraceae	Figs	Contact	Man	Action due to milky juice from stem
<i>Hypericum perforatum</i>	Hypericaceae	St. John's wort	Ingestion	Cattle and sheep	Active ingredients are fluorescent chemicals, hypericin and hypericum red
<i>Hypericum crispum</i>	Hypericaceae	.....	Ingestion	White sheep	
<i>Medicago denticulata</i>	Fabaceae	Bur clover	Ingestion	Cattle	
<i>Mentha citrata</i>	Labiatae	Bergamot mint	Contact	Man	
<i>Nolina texana</i>	Liliaceae	Bunch grass	Ingestion	Cattle	
<i>Tetradynamna canescens</i>	Compositae	Spineless horse bush	Ingestion	Cattle	
<i>Tetradynamna glabrata</i>	Compositae	Rabbit brush	Ingestion	Sheep	A resin-like ingredient causes "big head" of sheep
<i>Tribulus terrestris</i>	Zygophyllaceae	Puncture vine	Ingestion	Sheep	Causes "big head" of sheep (tribulosis)
<i>Trifolium hybridum</i>	Leguminosae	*Alslke clover	Contact	Man	

\* Human beings who have contacted photosensitizing plants or expect to contact them can prevent photosensitization dermatitis by applying to the exposed parts the formula given for workers with coal tar and other photosensitizing agents or by using the ordinary "sun tan" preparations. Painting white animals with tobacco juice or tannic acid is said to prevent photosensitization.

melanosis, which follows the course of the superficial blood vessels and is said to be caused by deposits of melanin.

#### PHOTOSENSITIVITY AND MELANOSIS DUE TO VITAMIN DEFICIENCIES

The lack of food containing a sufficient amount of vitamins may sometimes be the result of occupation. Sailors on ships making long journeys suffered with scurvy because of the lack of vitamin C in their diet. The English early recognized this and required that sailors be given a daily dose of lime juice, hence the term "limey" for English sailors. Nowadays scurvy can still be occupational among prisoners, explorers and those lost in the wilds, such as wrecked flyers. The hyperpigmentation of scurvy is due to perifollicular hemorrhage and is most prevalent on the anterior aspect of the thighs and upper part of the legs. Lack of vitamin A causes follicular keratoses, pigmented dry skin and night blindness. The lack of vitamin B<sub>2</sub> causes pellagra. The hyperpigmentation of pellagra occurs on the exposed parts first, resembling sunburn, but later there is thickening and desquamation and the erythema takes on a brownish hue. Melanosis of the exposed parts, called "war melanosis," occurring among Austrians during the first world war was described by Riehl. It was a perifollicular pigmentation attributed to deficiency of vitamin B complex from eating "ersatz" bread and to photosensitivity produced by eating photosensitizing plants.<sup>6</sup>

#### OCCUPATIONAL METALLIC DEPOSITS IN THE SKIN

Occupational deposits of metals in the skin which cause pigmentary changes are rare. Splinters of steel may become embedded in the skin of iron workers and specks of coal may be found in the skin of miners, but they are not sufficiently concentrated to constitute discoloration of any large areas. Deposits of iron in the skin have been reported from the use of ferrous sulfate and aluminum acetate in the treatment of ivy poisoning. Specks of silver forming bluish black spots may become embedded in the skin of workers with silver. Occupational argyria, a generalized pale blue discoloration of the skin, has been reported in Europe. White recorded several cases of occupational argyria: 1. in an old silver polisher, 1 in a worker who accidentally splashed himself with silver nitrate, in makers of artificial pearl beads, who formerly took into their mouths a weak solution of silver nitrate and blew it on the beads, 2 cases among handlers of silver leaf and 1 in a man who resilvered metal in a lathe.<sup>7</sup>

6. Becker, S. W., and Obermayer, M. E.: Modern Dermatology and Syphilology, Philadelphia, J. B. Lippincott Company, 1940.

7. White, R. P.: The Dermatoses, ed. 4, London, H. K. Lewis & Co., Ltd., 1934.

no cases of depigmentation of healed sites of occupational arsenical contact dermatitis have been reported.

Schwartz, Oliver and Warren<sup>10</sup> in 1940 reported an outbreak of occupational depigmentation of the skin among workers and others who wore yellow rubber gloves made by one company. They found that monobenzyl ether of hydroquinone, used as the antioxidant in the rubber, was the actual cause of the depigmentation. The depigmentation occurred on the hands, arms and places on the body where the gloves had come in contact with the skin. In the case of leather tanners who worked without shirts the antererior portions of the trunk where the gloves touched the skin were also affected. In some the depigmented areas were uniform and extensive, and in others the depigmentation was mottled. The hairs in the areas were not affected. It took several weeks to months after the gloves began to be worn for the depigmentation to appear. There were no inflammatory symptoms at any time. The depigmentation occurred in white persons and Negroes, but was most striking in the latter. Patch tests with the antioxidant remaining on the skin for seventy-two hours caused areas of leukoderma to develop three to five months after the patches were removed.

Several months after the use of the gloves was discontinued definite signs of returning pigment in the affected areas were noted. Repigmentation began around the hair follicles and spread peripherally, the areas coalescing, and was more rapid in some than in others. Three years afterward it was practically completed in all the cases. The report of a biopsy of patient J. T. made by Frederick D. Weidman was as follows:

A section showing repigmentation was stained with the dopa reagent. There was slight hyperkeratosis in one portion of the section. Acanthosis was negligible. Pigmentation was spotty in distribution and extreme in degree along a short extent of the epidermis. There was a rather singular occurrence; the pigment in the stratum corneum and the stratum granulosum tended to accumulate in a way that did not appear consistent with the amount of pigment in the basal layers—a distinctive appearance. In the deeply pigmented foci, pigmentation was greatest in the basal cell layer, with decided hyperpigmentation in the chromatophores in the tips of the dermal papillae. In the less pigmented areas there was also hyperpigmentation in these chromatophores. In general, there was no decided hyperpigmentation in the basal cell layer. The localization or distribution of the pigment was irregular, but even where the pigmentation was not heavy there were fine granules of pigment in the intercellular spaces. The dendritic cells were sharply outlined by powdery grains of pigment in their stellate processes, which extended far up into the epidermis. In all cases the pigment was extremely fine and powdery.

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10. Schwartz, L.; Oliver, E. A., and Warren, L. H.: Occupational Leukoderma, Pub. Health Rep. 55:1111-1130 (June 21) 1940.

The primary activity was in the chromatophores, which were present even around the sweat glands but were most abundant in the tips of the papillae and the blood vessels of the subpapillary layer. The dendritic cells in the epidermis had engulfed this pigment, thus accounting for its transportation upward into the epidermis. A rather unusual phenomenon was the accumulation of pigment in the stratum granulosum and, to a somewhat lesser extent, in the stratum corneum. The basal cells themselves were not the site of this production of pigment. In those places where the basal layer was pigmented intercellular location of the pigment was largely responsible. However, there were still small quantities of pigment in the cytoplasm. In the corium there was a diffuse tingeing of the collagen bundles in addition to the granules of pigment. In the sweat glands the cytoplasm of the secretory cells in particular and the collecting ducts to a less extent had excessively fine granular powdery pigment. The nuclei were not compromised except where the pigment was particularly dense, in which case the nucleus was somewhat pyknotic. There were no hair follicles or sebaceous glands in this section. Even the involuntary muscle around the sweat tubule was stained a diffuse brown. The arrectores pilorum and also the involuntary fibers in the vessel walls escaped involvement. In the lumens of the sweat glands was a rather shreddy, diffusely brown tinted material with some granules. One peculiar feature was the "backing up" or retention in the stratum granulosum of the aforementioned pigment.

A section of leukoderma and adjacent normal skin stained with hematoxylin and eosin showed the same characteristics as the aforementioned section; but the area of intense hyperpigmentation was more extensive, with lymphocytic proliferation around one blood vessel and a great number of chromatophores in the tips of the derma papillae. The pigment was intercellular in the basal layer and evidently located in the dendritic processes. The sweat gland cells showed a positive reaction to the dopa reagent (as noted in the previous section), but without pigment grains in these cells.

Summarizing the observations, the melanin pigment was present in chromatophores which occupy the dermal papillae and in the intercellular spaces of the basal layer of the epidermis. There were also small quantities of pigment within the cytoplasm of the basal cells. It was evident from the dopa reaction (in addition to the observations with hematoxylin and eosin staining) that the cells of the granular layer of the epidermis were dopa-positive. There were dopa-positive granules in the stratum corneum and in the secretory cells of the sweat glands.

The monobenzyl ether of hydroquinone is used as an antioxidant in light-colored acid-cured rubber goods because the acid cure (sulfur monochloride) does not affect monobenzyl ether of hydroquinone as much as it does other antioxidants and does not cause it to discolor. Experiments showed that this antioxidant can be dissolved out of rubber by perspiration. From the action of antioxidants in retarding the oxidation of rubber and from the report by Dr. Weidman one deduces that the monobenzyl ether of hydroquinone is dissolved out of the rubber by perspiration and absorbed into the skin where it prevents the combination of oxidase with the pigment precursor. Whether it does this by acting as a negative catalyst or whether it combines with the pigment precursor itself was not ascertained. The fact that repigmentation

occurred after the use of the gloves was discontinued shows that the chromatoblasts were not destroyed. The monobenzyl ether of hydroquinone in the skin was either completely oxidized or inactivated, or it was removed from the skin by catabolic processes.

Since the original report, there have been reported similar cases of decolorization of the skin among workers handling rubber in which monobenzyl ether of hydroquinone was used. There have also been reported several cases of depigmentation from rubber dress shields containing this chemical. Monobenzyl ether of hydroquinone is the only chemical ever reported to have caused occupational depigmentation of the skin without causing dermatitis.

infections. Other investigators also noted that areas of the cutaneous surface with a more alkaline  $p_H$  were more prone to invasion by pathogenic fungi.<sup>4</sup> None of these authors identified correctly the constituents of the sweat which were responsible for its  $p_H$ . Cornbleet<sup>5</sup> stated the belief that the skin had self-sterilizing powers which were not due to the surface acids.

It was pointed out by Peck and his associates<sup>1</sup> that the low  $p_H$  of the sweat was due to its content of volatile fatty acids and the  $p_H$  of the cutaneous surface was influenced by its covering of sweat. Changes in the  $p_H$  of the cutaneous surface could be produced by the action of bacteria, by the formation of salts of the fatty acids and by other factors. This point is important to the conception of the role of sweat as a protective mantle, since the fatty acids in sweat were shown to have an optimum  $p_H$  on the acid side for their fungistatic and fungicidal activity. In a recent publication, Herrmann and his co-workers<sup>6</sup> reemphasized that it is now generally agreed that the  $p_H$  of the surface of the skin is determined by the composition of the particular sweat and its residue.

While current interest in the fatty acids is focused mainly on their use as therapeutic agents, as far back as 1899 Clark<sup>7</sup> reported on the effects of fatty acids in the germination of molds. In 1913 Kiesel<sup>8</sup> had already demonstrated that the length of the carbon chain was important in determining fatty acid activity. He showed that saturated fatty acids increased in activity as the number of carbon atoms up to eleven increased and that the branched fatty acids were less active than those with straight chains and an equal number of carbon atoms.

Hoffman, Schweitzer and Dalby<sup>9</sup> in 1939 reported their studies on the fungistatic properties of the fatty acids on bread molds. They

4. Levin, O. L., and Silvers, S. H.: The Possible Explanation for the Localization of Ringworm Infection Between the Toes, Arch. Dermat. & Syph. 26:466-470 (Sept.) 1932.

5. (a) Cornbleet, T.: Disorders of the Feet as the Cause of Resistant Eczematoid Ringworm, Arch. Dermat. & Syph. 29:887-889 (June) 1934. (b) Cornbleet, T.: Selfsterilizing Powers of the Skin: Are They Endowed by the Surface Acid? ibid. 28:526-531 (Oct.) 1933.

6. Herrmann, F.; Behrendt, H., and Karp, F. L.: On the Acidity of the Surface of the Scalp and Other Areas of the Skin in Children, J. Invest. Dermat. 7: 215-226 (Oct.) 1946.

7. Clark, J. F.: On the Toxic Effect of Deleterious Agents on the Germination and Development of Certain Filamentous Fungi, Botan. Gaz. 28:277 and 378-402, 1899.

8. Kiesel, A., cited by Wyss, Ludwig and Joiner.<sup>10</sup>

9. Hoffman, C.; Schweitzer, T. R., and Dalby, G.: Fungistatic Properties of the Fatty Acids and Possible Biochemical Significance, Food Research 4:539-545 (Nov.-Dec.) 1939.

investigated the normal saturated fatty acids containing from one to fourteen carbon atoms over a  $p_H$  range from  $p_H$  2 to  $p_H$  8. The effectiveness varied according to the length of the chain and concentration of the acid as well as the  $p_H$  of the medium.

Peck and Rosenfeld<sup>2</sup> in 1938 reported their in vitro studies of the effects of the fatty acids on *Trichophyton gypseum*, the commonest fungus causing dermatophytosis, as well as their effects on *Epidermophyton inguinale* and (*Candida*) *albicans*. They reported on the fatty acid series with one carbon atom (formic acid) and concluded with capric acid with ten carbon atoms. The unsaturated undecylenic acid was also studied. A number of the sodium salts of the normal acids and some isoacids were also investigated for their fungicidal powers. There was no discernible relationship between the length of the carbon chain and the fungicidal properties of the fatty acids in the series studied. It seemed, however, that acids in the series higher than propionic with an odd number of carbon atoms were more fungicidal than those with even numbers. Wyss, Ludwig and Joiner<sup>10</sup> studied a number of saturated and unsaturated fatty acids and related compounds for their fungistatic and fungicidal activity. They observed that the long chain saturated and unsaturated fatty acids were superior to other acids and related derivatives both in their inhibition of fungi and in their killing of fungous spores.

Rothman and his co-workers<sup>11</sup> confirmed this last observation since they showed that acids with odd numbers of carbon atoms were more toxic for *Microsporon audouini* than the neighboring homologues with even numbers.

In the study by Peck and his associates<sup>1</sup> of the individual ingredients of the sweat fatty acids on the growth of fungi, the hydrogen ion concentration played an important role. For instance, the fungicidal properties rapidly decreased at a  $p_H$  above 6. This has an important bearing on the explanation of the effect of the  $p_H$  of the cutaneous surface on the susceptibility to infection. Fresh sweat has a low  $p_H$ , which is due to its content of volatile fatty, lactic and ascorbic acids. When the sweat becomes alkaline, it is due either to a decrease in the content of these acids or to the formation of their salts (sodium, calcium or ammonium). The formation of salts may be due to the interaction

10. Wyss, O.; Ludwig, B. J., and Joiner, R. R.: The Fungistatic and Fungicidal Action of Fatty Acids and Related Compounds, *Arch. Biochem.* **7**:415-425 (Sept.) 1945.

11. Rothman, S.; Smiljanic, A. M., and Shapiro, A. L.: Fungistatic Action of Hair Fat on *Microsporon Audouini*, *Proc. Soc. Exper. Biol. & Med.* **60**:394-395 (Dec.) 1945. Rothman, S.; Smiljanic, A.; Shapiro, A. L., and Weitkamp, A. W.: The Spontaneous Cure of *Tinea Capitis* in Puberty, *J. Invest. Dermat.*, to be published.

of the acids and substances on the surface of the skin, or the salts of the acids may be secreted as such by the sweat glands. It is also possible that ammonia is formed by the action of bacteria on urea and epithelium. This substance reacting with the acids may form ammonium salts (McSwiney). Whatever the explanation is, a natural buffer is formed on the cutaneous surface in areas of maceration and the like, which tends to form a more alkaline  $p_H$ . This alkaline  $p_H$  reduces the effectiveness of the fatty acids.

A review of the work of Minor,<sup>12</sup> Kuno,<sup>13</sup> Usher,<sup>14</sup> Sharlit and Scheer<sup>15</sup> and others<sup>16</sup> who studied the  $p_H$  of the cutaneous surface tends to show that the distribution of sweat on the surface of the body is closely bound to the  $p_H$  of the skin, and a comparison with areas where the common fungous infections tend to be localized shows that fungous infections usually do not tend to be initiated in areas of greatest concentration of true sweat. When the reverse occurs, we are dealing either with resistant types of fungi or, perhaps, with a disease mechanism which interferes with the normal protective action of the sweat mantle.

The role of the fatty acids might also explain the fungistatic power of blood serum, as has been investigated but never adequately explained by Peck, Rosenfeld and Glick,<sup>17</sup> Jessner and Hoffman,<sup>18</sup> Ayres and Anderson<sup>19</sup> and others and should now be reinvestigated from the viewpoint of its content of fatty acids.

#### CLINICAL EXPERIENCES WITH FATTY ACIDS

In their 1939 report, Peck and his co-workers<sup>1</sup> reported on the use of fatty acids in 51 cases of fungous infection, among which were tinea capitis, tinea versicolor, tinea cruris and dermatophytosis of the feet, with and without dermatophytids. They used 10 per cent sodium

12. Minor, V.: Ein neues Verfahren zu der klinischen Untersuchung der Schweißabsonderung, Zentralbl. f. d. ges. Neurol. u. Psychiat. **47**:800-803, 1927.

13. Kuno, Y.: The Physiology of Human Perspiration, London, J. & A. Churchill, Ltd., 1934.

14. Usher, B.: Human Sweat as a Culture Medium for Bacteria, Arch. Dermat. & Syph. **18**:276-280 (Aug.) 1928.

15. Sharlit, H., and Scheer, M.: The Hydrogen-Ion Concentration of the Surface of Healthy Intact Skin, Arch. Dermat. & Syph. **7**:592-598 (May) 1923.

16. Rothman, S., and Schoof, F.: Chemie der Haut, in Jadassohn, J.: Handbuch der Haut- und Geschlechtskrankheiten, Berlin, Julius Springer, 1929.

17. Peck, S. M.; Rosenfeld, H., and Glick, A. W.: Fungistatic Power of Blood Serum, Arch. Dermat. & Syph. **42**:426-437 (Sept.) 1940.

18. Jessner, M., and Hoffman, H.: Der Einfluss des Serums Allergiescher auf Trichophytonpilze, Arch. f. Dermat. u. Syph. **145**:187, 1923.

19. Ayres, S., Jr., and Anderson, N. P.: Inhibition of Fungi in Cultures by Blood Serum from Patients with "Phytid" Eruptions, Arch. Dermat. & Syph. **29**: 537 (April) 1934.

propionate in 50 per cent alcohol, 15 per cent sodium propionate in venetian talcum and 15 per cent sodium propionate in anhydrous wool fat and petrolatum as well as mixtures of various fatty acids in 50 per cent alcohol. The results were gratifying, especially in tinea cruris, tinea versicolor and dermatophytosis of the feet.

In 1943 Keeney<sup>20</sup> carried out extensive laboratory studies on the fungistatic activity of sodium propionate for various strains of pathogenic fungi. He also began preliminary clinical experiments with sodium propionate.

Keeney and his associates<sup>21</sup> then continued their work with the fatty acids. They investigated mixtures of propionic acid and the propionates in ointment form and compared their clinical effectiveness with that of undecylenate-undecylenic acid ointments in the treatment of tinea pedis as well as ointment of benzoic and salicylic acid, 10 per cent ammoniated mercury, 5 per cent sulfathiazole and 0.5 per cent tyrothrycin ointments. They came to the conclusion that the propionate-propionic acid ointment in vitro was superior to the other ointments in its fungistatic effect on *Trichophyton mentagrophytes*.

Furthermore, they apparently demonstrated that the propionate-propionic acid ointment in vitro was superior in its antibacterial effect on *Staphylococcus aureus* and B-hemolytic streptococcus to the previously mentioned ointments. In vitro the propionate-propionic acid ointment was as effective as penicillin ointment against B-hemolytic streptococcus (group A), but less effective against *S. aureus* (coagulase positive). The same authors also observed that the propionate-propionic ointment was superior to undecylenate-undecylenic acid ointment, in the treatment of tinea pedis.

Sulzberger and his associates<sup>22</sup> compared the efficacy of a number of foot powders in the treatment and prophylaxis of fungous infections

20. Keeney, E. L.: Fungistatic and Fungicidal Effects of Sodium Propionate and Common Pathogens, *Bull. Johns Hopkins Hosp.* **73**:379-390 (Nov.) 1943. Keeney, E. L., and Broyles, E. N.: Sodium Propionate in the Treatment of Superficial Fungous Infections, *ibid.* **73**:479-487 (Dec.) 1943.

21. (a) Keeney, E. L.; Ajello, L., and Lankford, E.: Studies on Common Pathogenic Fungi and on *Actinomyces Bovis*: In Vitro Effect of Fatty Acids, *Bull. Johns Hopkins Hosp.* **75**:377-392 (Dec.) 1944. (b) Keeney, E. L.; Ajello, L.; Lankford, E., and Mary, L.: Sodium Caprylate: A New and Effective Treatment for Dermatomycosis of the Feet, *ibid.* **77**:422 (Dec.) 1945.

22. Sulzberger, M. B.; Shaw, H. C., and Kanof, A.: Evaluation of Measures for Use Against Common Fungous Infections of the Skin: Screening Tests by Means of Paired Comparisons on Human Subjects, *U. S. Nav. M. Bull.* **45**: 237-248 (Aug.) 1945. Sulzberger, M. B., and Kanof, A.: Comparative Evaluation of Preparations for Prophylaxis and Treatment of Fungus Infections of the Feet, *ibid.* **46**:822-833 (June) 1946.

of the feet. Among the preparations tried were undecylenic acid-zinc undecylenate powder and calcium propionate powder. They concluded that the undecylenic powder was the most effective, although the calcium propionate powder was also effective.

Shapiro and Rothman<sup>23</sup> reported in 1945 that in the great majority of cases of dermatomycosis pedis, complete clinical cure could be achieved with the undecylenate preparation within four weeks. Relapses did not occur if treatment was continued. In tinea cruris and axillaris, complete clinical cure was accomplished also with undecylenate preparations. McCann<sup>24</sup> was also favorably impressed with the use of undecylenate preparations in fungous infections.

Fatty acid therapy was also tried by Keeney<sup>21b</sup> in 1945 in the treatment of infections due to *C. albicans* in the mouth (thrush) and in the vagina. The use of a 20 per cent solution of sodium caprylate adjusted to  $p_H$  7.4 and applied three or four times daily to the lesions in the mouth was effective.

Keeney also treated 2 patients with sporotrichosis with intramuscular injections and local applications of sodium undecylenate in 1 and with intravenous injections and local applications of sodium caprylate in the other. Although both fatty acids were observed by Keeney (1944) to be effective in vitro against *Sporotrichum schenckii*, neither patient responded to the treatment.

The clinical effectiveness of sodium caprylate was further investigated by Keeney and his associates<sup>25</sup> in dermatomycosis of the feet. They observed that 10 per cent sodium caprylate was superior in vitro to propionate-propionic acid ointment, 5 and 10 per cent undecylenate-undecylenic acid ointment, ointment of benzoic and salicylic acid, 10 per cent ammoniated mercury, 5 per cent sulfathiazole and 0.5 per cent tyrothricin ointment against *T. mentagrophytes*. It was inferior, however, to propionate-propionic acid and 5 per cent sulfathiazole ointment in in vitro antibacterial effect against *S. aureus*. The sodium caprylate ointment was also inferior to propionate-propionic acid ointments and undecylenate-undecylenic acid ointments in in vitro antibacterial effect against *B. hemolytic streptococcus* (group A).

The clinical results with a 10 per cent sodium caprylate ointment in the treatment of dermatomycosis of the feet was significantly superior

23. Shapiro, A. L., and Rothman, S.: Undecylenic Acid in the Treatment of Dermatomycosis, Arch. Dermat. & Syph. **52**:166-171 (Sept.) 1945.

24. McCann, W.: Treatment of Skin Diseases on an Attack Transport: Use of Undecylenic Acid, U. S. Nav. M. Bull. **43**:1205-1207 (Dec.) 1944.

25. Keeney, E. L.; Lankford, E.; Ajello, L., and Mary, L.: The Bacteriostatic and Bactericidal Effects of Fatty Acid Salts on Bacteria in Broth Cultures, Bull. Johns Hopkins Hosp. **77**:437-439 (Dec.) 1945. Keeney, Ajello, Lankford and Mary.<sup>21b</sup>

to those results previously obtained with either propionate-propionic acid or undecylenate-undecylenic acid ointments.

In 1946, Hopkins and his co-workers<sup>26</sup> reported on their extensive investigations on the evaluation of fungistatic agents for the treatment of dermatophytosis. A significant observation was that almost any nonirritating fungicide caused gradual improvement in most cases of dermatophytosis. Furthermore, they noted that attempts to kill fungi by application of a powerful fungicide rarely seemed to accelerate cures and frequently caused disastrous irritation.

Undecylenic acid preparations gave a higher percentage of satisfactory clinical results than propionic acid preparations. They, too, emphasized the importance of secondary infection with streptococci or staphylococci as part of the clinical picture of dermatophytosis.

Hopkins and his co-workers tried 10 per cent sodium caprylate in a small series of cases. There seemed to be a greater percentage of improvement in the first two weeks of treatment than was seen with the undecylenic acid preparations. They observed that while the propionic acid preparations gave a lower over-all percentage of satisfactory results than did the undecylenic acids, they seemed to approximate the latter in clinical effectiveness. The results obtained with propionic acid in tinea cruris were superior to those obtained with undecylenic acid. Furthermore, undecylenic acid also was more irritating than the propionic, especially when applied to the groin or body. This has been our experience also.

Rothman and his associates<sup>11</sup> have recently cast a great deal of light on the mechanism which is responsible for the spontaneous cure of ringworm in the postpuberty period. They stated the belief that with the onset of puberty the sebaceous glands of the scalp start to secrete a sebum which contains higher concentrations of low-boiling saturated fatty acids, with selective fungistatic and fungicidal action on *M. audouini*. They were able to isolate from "hair fat" of adults highly active normal aliphatic monobasic acids, including pelargonic, having odd numbers of carbon atoms. In addition, in a personal communication Rothman informed us that he had also identified tridecanoic acid ( $C_{13}$  straight chain saturated acid). This acid was as fungistatic as was pelargonic on *M. audouini*.

#### IN VITRO AND IN VIVO EXPERIENCES WITH MIXTURES OF PROPIONATES AND CAPRYLATES

Since Keeney and his group as well as Hopkins and his associates had reported favorably on sodium caprylate in the treatment of fungous

26. Hopkins, J. G.; Hillegas, A. B.; Ledin, R. B.; Rebell, J. C., and Camp, E.: Fungistatic Agents for Treatment of Dermatophytosis, *J. Invest. Dermat.* 7: 239-253 (Oct.) 1946.

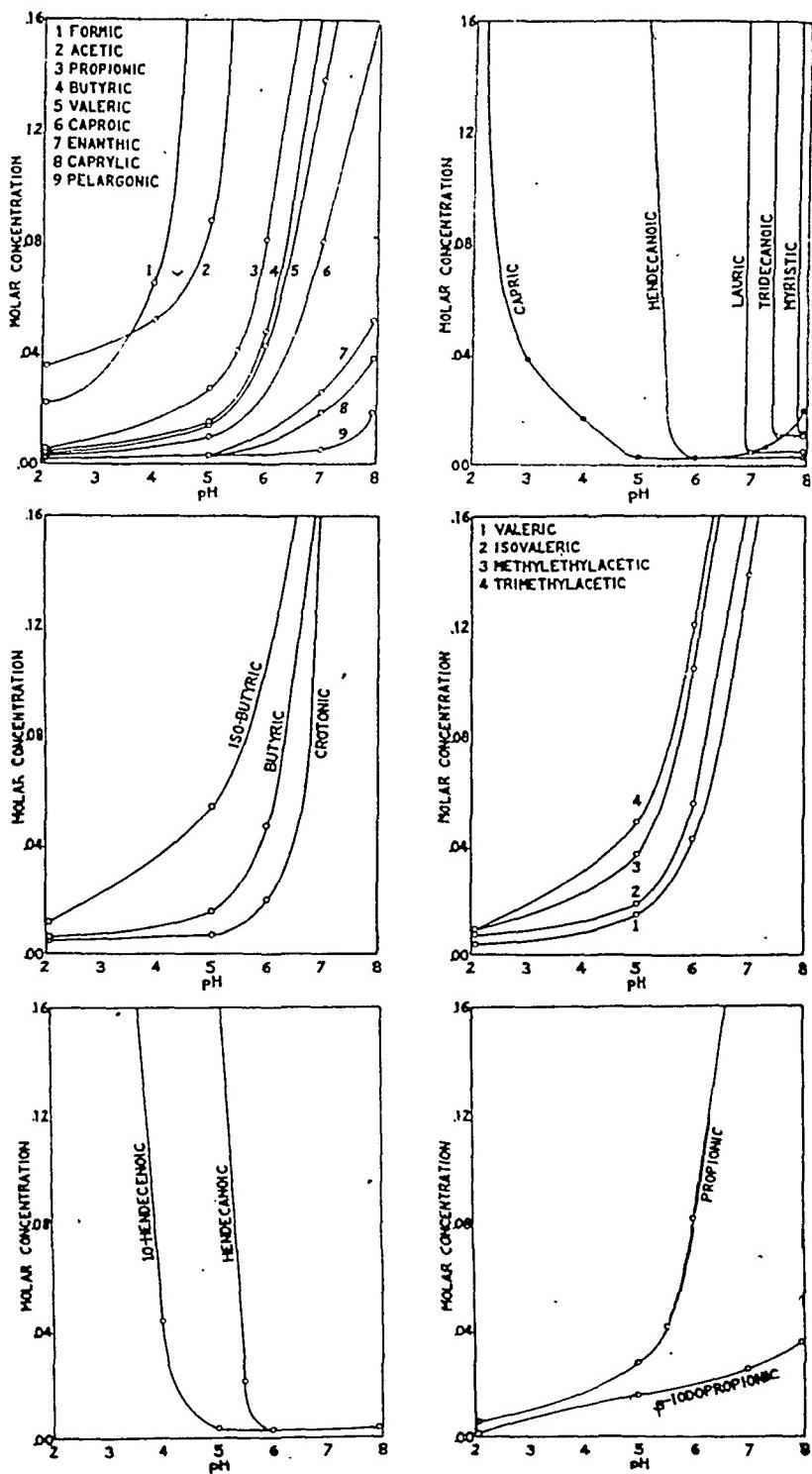


Fig. 1.—The graphs show the fungistatic activity of the fatty acids containing from 1 to 14 carbon atoms at various  $p_H$  values. These curves are a composite against several nonpathogenic and pathogenic fungi and are based on the minimal molar fatty acid content to inhibit growth of the organism for seventy-two hours at 37 C. in agar plate (nutrient agar plus 1 per cent dextrose and buffer solution).

infections, it was thought that it might be of value to study propionate-caprylate mixtures in vitro and in vivo, especially since both acids are found in human sweat.

*Materials Used.*—*T. mentagrophytes* (Conant strain 1919) was used in the experiment. One cubic centimeter of a spore suspension was seeded through 5 cc. of nutrient agar (one and one-half strength). Five cubic centimeters of McIlvaine's buffer solution double strength

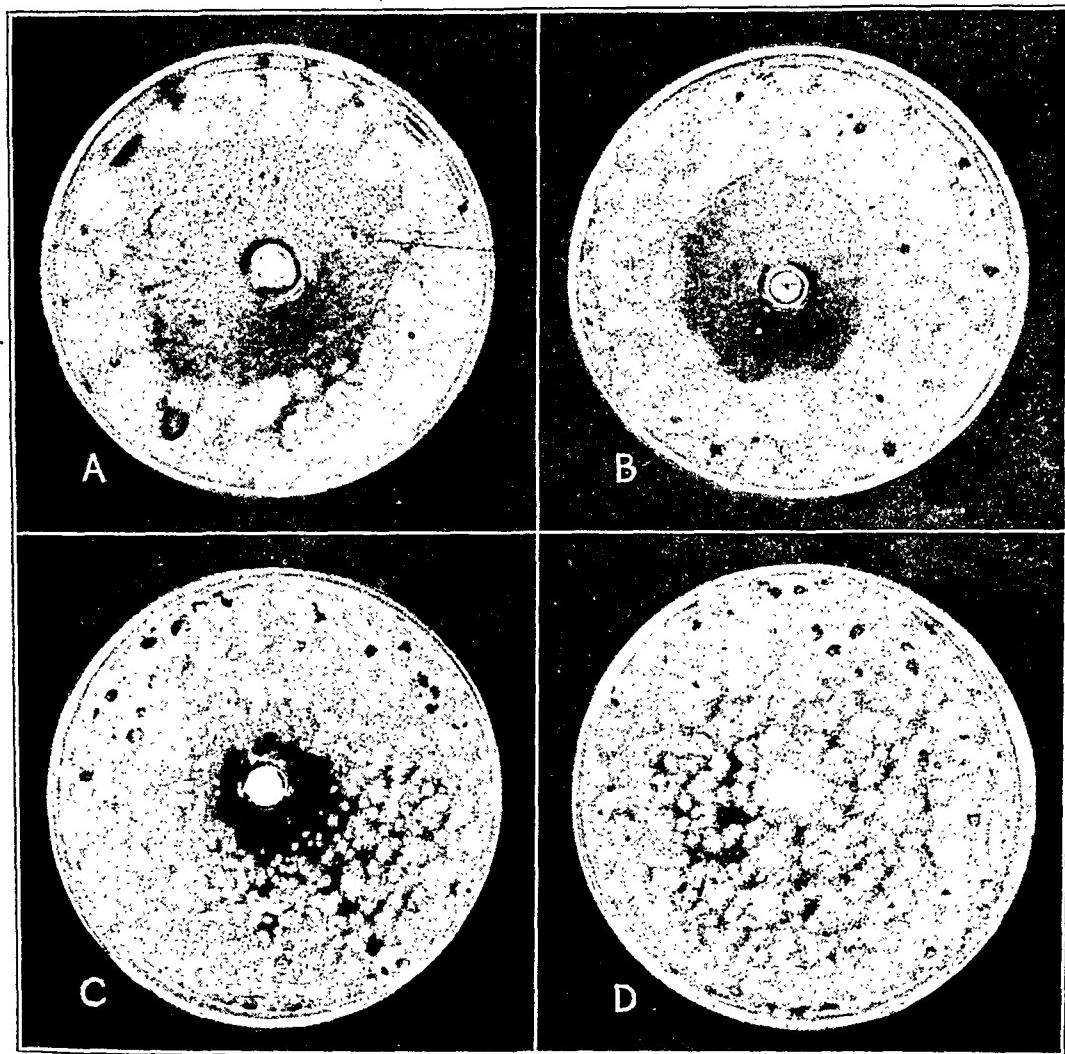


Fig. 2.—The effect of propionates and caprylates on the growth of *T. mentagrophytes* at 37 C. for seventy-two hours. In *A*, propionates and caprylates were used; in *B*, caprylates alone were used; in *C*, the propionates alone were used, and in *D*, the control with the ointment base was used.

was added ( $p_H$  5.5). The fungistatic action of the test material was investigated by the agar cup method. In figure 2 *A*, there were used as active ingredients 12.3 per cent sodium propionate, 2.7 per cent propionic acid and 10 per cent sodium caprylate incorporated in an ointment base; in figure 2 *B* there was used 10 per cent sodium caprylate incorporated in an ointment base; in figure 2 *C* there were

used 16.4 per cent sodium propionate and 3.6 per cent propionic acid incorporated in an ointment base, and in figure 2 *D* there was used the control ointment base alone in which were incorporated the inactive ingredients used in *A*, *B* and *C*. The plates were incubated at 37 C. for seventy-two hours.

*Results.*—Figure 2 depicts results at the end of seventy-two hours. The superiority of the propionate-caprylate mixture, as far as can be judged by the zone of inhibition around the agar cup, can be clearly seen.

The results are interesting in view of the observations of Hoffman, Schweitzer and Dalby,<sup>27</sup> who showed that when a weak fungistat and a strong one are mixed, the weaker fungistat inactivates the stronger. These investigators showed that when acetic acid is mixed with caprylic in equimolecular proportions, approximately 50 per cent of the stronger fungistat, that is, caprylic, is inactivated. However, when two active fungistats, such as propionic and caprylic acids, are mixed, there is an increased fungistatic effect, regardless of whether the acids tested are in aqueous solution or in a water-soluble ointment base (as shown in fig. 2).

The aqueous solutions, when tested by the same agar cup plate method, gave the following results at  $p_H$  5.5:

20.0% propionic acid.....	0.2 cc.	3.4 cm. zone
5.3% caprylic acid.....	0.2 cc.	2.5 cm. zone
10.0% propionic acid.....	{ 0.2 cc.	4.0 cm. zone
2.65% caprylic acid.....		

#### CLINICAL EXPERIENCES WITH PROPIONATE-CAPRYLATE MIXTURES

The patients reported on here were treated with an ointment having the following active ingredients: 12.3 per cent sodium propionate, 2.7 per cent propionic acid and 10 per cent sodium caprylate in an ointment base. In most instances microscopic or cultural evidence of fungous infection could be demonstrated. In a number of instances, especially in tinea of the hands and feet, there was only clinical evidence for the diagnosis.

*Tinea Cruris.*—There were 19 cases in this group. A number of the patients had been treated previously with other fungicides. Clinical improvement was judged by the disappearance of itching and the rapid clearing of the vesicles and scales. There was rapid and striking improvement in the majority by the end of the second week and in nearly all by the end of the third week. When there was coincidental dermatomycosis around the rectum it took much longer to obtain a clinical cure, in many instances several months.

27. Hoffman, C.; Schweitzer, T. R., and Dalby, G.: Fungistatic Properties of Binary Fatty Acid Mixtures, *J. Am. Chem. Soc.* **63**:1472-1473 (May) 1941.

*Tinea Glabrosa.*—There were 12 patients in this group, including a number of children. In most, *T. gypseum* could be identified as the causative fungus. There were several children with infection with *M. audouini*. The great majority of the patients were cured in two weeks, and in 2 it took somewhat longer. There was no instance in which the infection failed to clear up completely.

*Tinea of the Rectum.*—The most striking effect was on pruritus. Itching subsided quickly even when there was eczematization. Of the 5 patients in this group, 3 were free of symptoms in six weeks and 2 still showed clinical evidence of activity after two months of treatment, but the pruritus was controlled.

*Tinea of the Nails.*—No topical application is efficacious unless it is combined with some method of mechanical burring of the nails. Ten patients were treated in this series. The patients were seen once a week. At each visit an electric drill was used to grind down the surface of the nail as much as possible, that is, until the patient complained of pain. The patients were then instructed to rub the ointment into the affected nail twice a day. They were also told to file the surface of the nail at home with emery paper as much as possible before each application of the ointment. It took months of treatment to effect a cure. Six patients were apparently cured and showed no recurrence in several months of follow-up. Two of these patients seemed clinically cured in two months, 3 were cured in three months and 1 in five months. The other 4 were under continuous treatment for six to eight months, with improvement in some instances but evident continuation of the infection. *Trichophyton purpureum* was responsible for the infection in all 4 patients for whom treatment failed. However, there were several patients with *purpureum* infection among those considered cured.

*Tinea of the Hands and Feet.*—Patients with this condition composed the largest group studied. There were 73 patients with *tinea pedis*, some with "ids" on the hands. There were 13 cases of definite fungous infection of the hands.

It is difficult to declare that there is complete cure in a case of *tinea pedis*. Even when there is a clinical cure it is sometimes possible to culture pathogenic fungi after the cessation of treatment. Also, if the treatment is not continued after a clinical cure has been obtained, there is certain to be a recurrence sooner or later. The criterion for cure in our series was the complete disappearance of itching, scales and vesicles.

Our results in these cases could be summarized as follows: 1. There was striking improvement in the first two weeks in the majority of cases, much more rapid than was observed in similar cases with

the propionates or caprylates alone. 2. Itching was controlled much faster than with any preparation hitherto used. In 25 per cent of the cases the itching was controlled in the first week, and in 50 per cent of the cases the itching had disappeared by the end of the second week with definite clinical improvements. 3. Seventy-five per cent of the patients were considered clinically cured by the end of four to five weeks of treatment. 4. In at least one half of the remaining 25 per cent there was decided improvement by the end of the fifth week, but there was still some evidence of activity as indicated by scaling. 5. There was a rapid disappearance of "ids." 6. In those considered clinically cured there was no recurrence if treatment was continued once or twice a week as a prophylactic measure.

*Proved T. Purpureum Infection of the Glabrous Skin or of the Hands and Feet, Exclusive of the Nails.*—There were 5 patients in the group with T. purpureum infection of the glabrous skin or of the hands and feet, exclusive of the nails: One was a female patient with lesions on the body which had been present for many months. At the end of three weeks of treatment the lesions had practically disappeared. One was a female patient with extensive lesions on the body—three months of treatment resulted in disappearance of lesions. The third was a male patient whose infection was limited to the hands and feet and who was practically well at the end of three months of treatment. The fourth was male, with involvement limited to the feet, who had used propionate-propionic acid and caprylate preparations separately for many weeks, with continuous recurrences. At the end of two months of treatment with the mixture there was a clinical cure. The fifth was a male patient, with infection of the feet, in whom there was improvement following the use of propionate-propionic acid mixture for three months, but there was still clinical activity. It took another three months of the daily use of propionate-caprylate ointment to obtain a clinical cure.

We realize that one might validly say that if any one of the previous fungicides had been used long enough it also might have resulted in apparent cure. However, some of the previous methods of treatment had been used for months, without any appreciable results.

*Irritation.*—There were only 2 instances of irritation encountered in all the patients treated. Both patients had a decidedly positive reaction in the trichophytin test. There was irritation in the form of increased itching and a flare-up of the lesions in the beginning of the treatment. The concentration of the ointment was decreased to one third and gradually increased in strength until, finally, it could be used again in its full strength. In both, there was no irritation when it was used on the feet, but only on the eczematized "ids" of the hands.

## SULFAPYRIDINE IN THE TREATMENT OF DERMATITIS HERPETIFORMIS

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DERMATITIS herpetiformis has challenged the therapeutic ingenuity of physicians since it was first described by Duhring<sup>1</sup> in 1884. Until the advent of sulfonamide drugs the therapeutic endeavors of dermatologists consisted of giving some form of inorganic arsenic, such as solution of potassium arsenite and "Asiatic pills" (contain arsenous acid and black pepper) by mouth and sodium arsenate by subcutaneous injection. Other measures, such as the application of sulfur ointment, autohemotherapy, intestinal antisepsis by high colonic irrigation, catharsis and the removal of foci of infection were attended with indifferent results.

For many years dermatitis herpetiformis was thought by many to be the cutaneous expression of bacterial allergy. It was with this in mind that physicians welcomed the opportunity to try the sulfonamide drugs in the treatment of this inveterate dermatosis.

Dostrovsky and his associates<sup>2</sup> concluded from experimental work on animals that dermatitis herpetiformis was caused by some filterable virus belonging to a group of neuropathic viruses. Pillsbury<sup>3</sup> presented a case of a 2½ year old white child in whom hemolytic streptococci and *Staphylococcus aureus* were seen in the culture from the vesicles. McDonald<sup>4</sup> observed that the level of vitamin C in the blood was depressed in dermatitis herpetiformis. He studied a patient who had a depressed level of vitamin C in the blood when he had a recurrence or exacerbation of this disease and a normal determination when he was free of the eruption. The patient improved when he took 1,000 mg. of ascorbic acid orally each day. Cannon<sup>5</sup> stated that the only patients

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1. Duhring, L. A.: Dermatitis Herpetiformis, *J. A. M. A.* **3**:225 (Aug. 30) 1884.
2. Dostrovsky, A.; Gurevitch, I., and Ungar, H.: On the Question of the Etiology of Pemphigus Vulgaris and Dermatitis Herpetiformis, *Brit. J. Dermat.* **50**:412 (Aug.-Sept.) 1938.
3. Pillsbury, D. M.: Dermatitis Herpetiformis, *Arch. Dermat. & Syph.* **38**: 985 (Dec.) 1938.
4. McDonald, F.: Dermatitis Herpetiformis, *Arch. Dermat. & Syph.* **40**:844 (Nov.) 1939.
5. Cannon, A. B., in discussion on Hopkins.<sup>36</sup>

suffering with dermatitis herpetiformis in whom he had observed permanent cures were those in whom foci of infection were found and eliminated. He wrote of 3 cases of spectacular cures, in 2 after extraction of abscessed teeth and in the third after cure of pyelonephrosis. In each case improvement was noticed immediately after the removal of the focus of infection, and within a few weeks all symptoms had disappeared. Weidman<sup>6</sup> also suggested that investigations be made for focal infections. One of his patients who had suffered from dermatitis herpetiformis was observed at necropsy to have bronchiectasis, which had escaped notice. In spite of the fact that foci of infection are searched for, when they are found and removed the eruption is not frequently alleviated or cured.

Investigations by Bernhardt<sup>7</sup> and others have demonstrated cutaneous hypersensitivity to many types of bacterial extracts, namely, staphylococcic and streptococcic vaccines, tuberculin and trichophytin. Swartz and Lever<sup>8</sup> noted that the intradermal injection of autogenous colon bacillus vaccine produced grouped papulovesicular reactions resembling in form the early lesions of this disease. De Oreo<sup>9</sup> treated twin men, aged 25, who had had dermatitis herpetiformis for twenty-six months. They had been separated by miles, but when they met after an absence of three months, each noticed that the other had an eruption similar to his own. Patch tests with potassium iodide ointment elicited positive reactions. Ten minims (0.6 cc.) of the saturated solution of potassium iodide was administered orally three times a day to 1 twin. There was an exacerbation of the eruption. De Oreo stated that dermatitis herpetiformis may be the result primarily of possible ectodermal defect rather than an infectious process. Sulfapyridine was administered to 1, with good therapeutic response.

Whitby<sup>10</sup> in 1938 reported that sulfapyridine (2-sulfanilylaminopyridine, synthesized by Evans and Phillips in the chemical research laboratories of May and Baker, Ltd., Dagenham, England) was effective in the treatment of pneumococcic infections in mice. Evans and Gaisford<sup>11</sup> determined its value in the treatment of lobar pneumonia. It

6. Weidman, F., in discussion on Pratt, A. G.: Dermatitis Herpetiformis Followed by Lesions Resembling Lichen Planus, *Arch. Dermat. & Syph.* **53**:665 (June) 1946.

7. Bernhardt, R.: Weitere Beitrage zur Aetiologie des Pemphigus und der Duhringschen Krankheit, *Arch. f. Dermat. u. Syph.* **171**:536, 1935.

8. Swartz, J. H., and Lever, W. F.: Dermatitis Herpetiformis: Immunologic and Therapeutic Considerations, *Arch. Dermat. & Syph.* **47**:680 (May) 1943.

9. De Oreo, G. A.: Dermatitis Herpetiformis Occurring in Twins, *Arch. Dermat. & Syph.* **54**:360 (Sept.) 1946.

10. Whitby, L. E. H.: Chemotherapy of Pneumococcal and Other Infections with 2-(p-Aminobenzenesulfonamido) Pyridine, *Lancet* **1**:1210 (May 28) 1938.

11. Evans, G. M., and Gaisford, W. F.: Treatment of Pneumonia with 2-(p-Aminobenzenesulphonamido) Pyridine, *Lancet* **2**:14 (July 2) 1938.

was referred to by its laboratory serial number, "M. & B. 693." The drug was given the same "dagenan." Sulfapyridine was introduced into the United States during the winter of 1938-1939 and was used in the treatment of pneumonia.

Sulfapyridine (Merck & Co., Inc.) is a white crystalline powder with a melting point at 190.5 to 191.5 C. It is related to the parent compound sulfanilamide. It is soluble in water (28 mg. in 100 cc. at 27.5 C.). Its solubility is thirty times less than that of sulfanilamide.

Sulfanilamide was tried in the treatment of dermatitis herpetiformis and found wanting by many. However, Caro<sup>12</sup> had successfully treated a patient with pemphigus with sulfanilamide, and Lain and Lamb<sup>13</sup> obtained a spectacular cure of a pemphigoid eruption with sulfanilamide. Swartz and Lever<sup>8</sup> reported that a review of the American literature up to 1941 indicated that sulfanilamide had been used successfully in the majority of the patients suffering with dermatitis herpetiformis, but the response had been temporary.

Sulzberger<sup>14</sup> treated a woman with sulfapyridine for acrodermatitis continua (Hallopeau). The temporary beneficial effects of sulfapyridine were illustrated.

In 1938, I treated a single woman, aged 20 and of Italian descent, who had been suffering from severe extensive dermatitis herpetiformis for three years. She had pneumonia in 1934, for which she received antipneumococcic serum. Following this illness she suffered from discharging chronic otitis media. The patient had a typical eruption of dermatitis herpetiformis, but in addition she had vesicles and bullae on the conjunctival sac and the nasal, oral and vaginal mucous membranes. She had received solution of potassium arsenite, sulfur ointment, autohemotherapy, roentgen irradiation, sodium cacodylate intravenously, autogenous vaccine made from the stool (*Streptococcus viridans* and nonhemolytic *Bacillus coli*), vaccination against smallpox and sedatives, without favorable effect on the eruption. A severe exacerbation of the eruption followed vaccination against smallpox. In April 1938, sulfanilamide, 1.0 Gm. every four hours, was administered for ten days, without favorably affecting the pruritus or the eruption. In the winter of 1938-1939, sulfapyridine (2-sulfanilylaminopyridine, "M. & B. 693 *dagenan*") became available in New York. I<sup>15a</sup> pre-

12. Caro, M. R.: Pemphigus: Treatment with Sulfanilamide, *Arch. Dermat. & Syph.* **37**:196 (Feb.) 1938.

13. Lain, E. S., and Lamb, J. H.: Treatment of a Pemphigoid Eruption with Sulfanilamide, *Arch. Dermat. & Syph.* **37**:840 (May) 1938.

14. Sulzberger, M. B.: Effect of Treatment with Sulfapyridine on Acrodermatitis Continua (Hallopeau) *Arch. Dermat. & Syph.* **40**:853 (Nov.) 1939.

15. Costello, M. J.: (a) Dermatitis Herpetiformis Treated with Sulfapyridine, *Arch. Dermat. & Syph.* **41**:134 (Jan.) 1940; (b) Dermatitis Herpetiformis Treated Successfully with Sulfapyridine, *ibid.* **42**:161 (July) 1940.

1 submitted a confidential reply, 5 had tried no sulfonamide drug other than sulfapyridine and 1 member had no definite information. Approximately 90 per cent of the members who had used the sulfonamide drugs in the treatment of dermatitis herpetiformis answered that sulfapyridine was the sulfonamide drug of choice. In reply to question 3—If not (sulfapyridine), which sulfonamide drug do you prefer in the treatment of this disease?—59 stated that they preferred sulfapyridine, 3 preferred sulfadiazine, 1 preferred sulfanilamide; 11 gave indefinite answers, 23 had little or no experience, 2 stated that sulfapyridine and sulfadiazine were of equal value and 1 had given only sulfaguanidine to 2 patients: 1 had improved, and 1 had becomes worse. Ninety per cent of the members who had experience with the sulfonamide drugs preferred sulfapyridine. In reply to question 4—What is your initial dose and what is your maintenance dose?—the answers varied from 0.5 to 6.0 Gm. daily for the initial dose, averaging approximately 1.0 Gm. three times a day, and for the maintenance dose from 0.5 to 4.0 Gm. daily, averaging approximately 0.5 Gm. three times a day. In reply to question 5—Have any of the patients been cured?—of 96 members, 9 answered that they had patients who had been cured, 55 replied in the negative, 9 gave indefinite answers and 23 had little or no experience. Twelve per cent of those who had experience with the sulfonamide drugs in the treatment of dermatitis herpetiformis had patients who were cured with this drug. In reply to question 6—How many have improved?—22 of 100 stated that all the patients treated had improved, 27 stated that, on the average, approximately 62 per cent had improved, 23 stated that the patients had improved but did not give the number or percentage, 23 had little or no experience and 5 were noncommittal. Of those who had experience with the sulfonamide drugs 100 per cent stated that, on the average, 80 per cent of the patients had improved. In reply to question 7—Do you believe that the suffering caused by this chronic disease warrants the use of a sulfonamide drug?—68 of 100 answered yes, 9 answered no and 23 did not have sufficient experience to justify an opinion in the matter. Of those who had experience with the sulfonamide drugs 89 per cent answered "yes" to this question. In reply to question 8—Do you think that it is a therapeutic test for dermatitis herpetiformis?—33 of 100 answered yes, 30 answered no, 14 were doubtful and 23 did not have sufficient experience. In reply to question 9—In your experience what is the longest period of continued treatment with this drug?—of 100 members 1 answered that he had administered the drug from six to seven years, 1 for five years, 2 for four years, 8 for three years, 9 for two years, 5 for one and a half years and 8 for one year, making a total of 34 members who had administered the drug for a year or more. One physician administered the drug for eight months, 9 for six months,

in the number of cells. (5) Hepatitis and jaundice are rare. (6) Disturbances of the central nervous system include headache, malaise, vertigo, mental depression and (rarely) excitement severe enough to be classified as toxic psychosis. Extreme restlessness has been encountered. Severe toxic effects include granulocytopenia, or neutropenia, and acute hemolytic anemia. The majority of reports tend to support the idea that severe dyscrasias of the blood follow the administration of large initial doses of sulfapyridine, but numerous reports on this phase of the subject indicate that severe changes in the blood may follow only relatively small amounts of sulfapyridine, especially when administered on a second occasion. It cannot be too strongly emphasized that blood cell and platelet counts and urinalyses should be made before and at intervals during treatment and for several weeks after treatment has been discontinued. There is less danger of toxic reactions after four to six weeks. Hellerstrom<sup>22</sup> reported that he had a patient in whom agranulocytopenia developed and who died after the use of sulfapyridine for dermatitis herpetiformis.

A number of the patients whom I have observed during treatment with sulfapyridine have presented initial lowering of the leukocyte count, with moderate leukopenia, and red blood cells in the urine. These reactions are usually not progressive; they either remain stationary or improve. Formation of calculi in the urinary tract has been observed. Hematuria has been encountered frequently and reported by Southworth and Cooke.<sup>23</sup> There is usually acute pain in the abdomen, of renal or ureteral origin. Long and Wood<sup>24</sup> encountered in their series of 100 cases 1 case which terminated fatally. Analysis of these small calculi reveals 85.6 per cent acetylsulfapyridine and 0.6 per cent sulfapyridine. Acetylsulfapyridine, being poorly soluble, tends to precipitate out in the urine. Frequently, patients complain of some loss of appetite and of weakness and may look pale for a considerable period. The aforementioned changes are not contraindications to treatment, but these patients should be closely watched.

Patients under treatment for dermatitis herpetiformis with sulfonamide drugs should be advised against driving automobiles, especially on long trips, or any other hazardous occupation which necessitates a high degree of mental alertness and manual dexterity.

Numerous reports in the literature prove that all the popular sulfonamide drugs have been used successfully in the treatment of dermatitis

22. Hellerstrom, S.: Personal communication to the author.

23. Southworth, H., and Cooke, C.: Hematuria: Abdominal Pain and Nitrogen Retention Associated with Sulfapyridine, *J. A. M. A.* **112**:1820 (May 6) 1939.

24. Long, P. H., and Wood, W. B., Jr.: Observations upon Experimental and Clinical Use of Sulfapyridine: II. Treatment of Pneumococcal Pneumonia with Sulfapyridine, *Ann. Int. Med.* **13**:487 (Sept.) 1939.

herpetiformis. Lewis,<sup>25</sup> Butterworth,<sup>26</sup> Abramowitz<sup>27</sup> and others have administered sulfanilamide with success. Costello,<sup>16</sup> Oliver and Cohen,<sup>28</sup> Senear and Perlstein,<sup>29</sup> Brunsting<sup>30</sup> and Ingram<sup>31</sup> have obtained good results in the treatment of dermatitis herpetiformis with sulfapyridine. Costello,<sup>32</sup> Costello, Rubinowitz and Landy,<sup>33</sup> Van Dyck,<sup>34</sup> Cipollaro<sup>35</sup> and Hopkins<sup>36</sup> controlled the disease in their patients with sulfathiazole. Lewis<sup>37</sup> reported a patient who had herpes gestationis which was successfully controlled with small doses of sulfathiazole. He expressed the belief that this result was further evidence that herpes gestationis was dermatitis herpetiformis of pregnancy. I have been able to confirm these observations in herpes gestationis on several occasions. Carpenter and Hall<sup>38</sup> treated with penicillin 6 naval personnel members between the ages of 20 and 32 years. They had previously received sulfapyridine, which had been of great benefit to all. There was rapid improvement in all patients while they were receiving injections of penicillin, which the authors thought substantiated the theory that this disease is a form of bacterial allergy rather than a disease of neurogenic or metabolic origin. There was prompt recur-

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- 25. Lewis, G. M.: Dermatitis Herpetiformis (Treated with Sulfanilamide): Arsenical Keratoses, *Arch. Dermat. & Syph.* **42**:961 (Nov.) 1940.
  - 26. Butterworth, T., in discussion on Schildkraut, J. A.: A Case for Diagnosis (Duhring's Disease?), *Arch. Dermat. & Syph.* **40**:650 (Oct.) 1939.
  - 27. Abramowitz, E. W., in discussion on Lewis.<sup>25</sup>
  - 28. Oliver, E. A., and Cohen, T. M.: Dermatitis Herpetiformis, *Arch. Dermat. & Syph.* **44**:303 (Aug.) 1941.
  - 29. Senear, F. E., and Perlstein, M., in discussion on Omens, D. V.: Dermatitis Herpetiformis, *Arch. Dermat. & Syph.* **43**:1065 (June) 1941.
  - 30. Brunsting, L., in discussion on Mitchell, J. J., and Hetreed, F. W.: A Case for Diagnosis (Dermatitis Herpetiformis?), *Arch. Dermat. & Syph.* **45**:1197 (June) 1942.
  - 31. Ingram, J. T.: Advances in the Treatment of Diseases of the Skin, *Practitioner* **143**:398 (July-Dec.) 1939.
  - 32. Costello, M. J.: Dermatitis Herpetiformis Controlled with Sulfathiazole, *Arch. Dermat. & Syph.* **45**:226 (Jan.) 1942.
  - 33. Costello, M. J.; Rubinowitz, A. M., and Landy, S. E.: Sulfonamide Therapy in Dermatology: Observations in Two Hundred and Sixty-One Cases at Bellevue Hospital, New York State J. Med. **42**:2309 (Dec. 15) 1942.
  - 34. Van Dyck, L. S.: Dermatitis Herpetiformis: Results of Treatment with Sulfathiazole, *Arch. Dermat. & Syph.* **45**:405 (Feb.) 1942.
  - 35. Cipollaro, A. C., in discussion on Van Dyck.<sup>34</sup>
  - 36. Hopkins, J. G.: Dermatitis Herpetiformis, *Arch. Dermat. & Syph.* **45**:1000 (May) 1942.
  - 37. Lewis, G. M.: Herpes Gestationis: Report of a Case, *Arch. Dermat. & Syph.* **46**:841 (Dec.) 1942.
  - 38. Carpenter, C. C., and Hall, W. H., Jr.: Treatment of Dermatitis Herpetiformis with Penicillin, *Arch. Dermat. & Syph.* **51**:241 (April) 1945.

rence of the disease when the treatment with injections of penicillin was terminated. Failure of penicillin in treatment of dermatitis herpetiformis has also been reported. Park<sup>39</sup> treated a soldier with 480,000 units of penicillin; he failed to respond, but his eruption promptly cleared up with sulfapyridine.

Some failures in the treatment of dermatitis herpetiformis with sulfapyridine occasionally occur because the initial doses are not sufficiently large to be immediately effective. It is important that the initial doses be adequate for prompt action and that the dose be reduced to the effective minimum after the therapeutic effect is obtained.

Recently, Lehr<sup>40</sup> claimed that the sulfonamide drugs are less toxic and more soluble if given in combination in the treatment of infection. He administered a mixture of at least two of the sulfonamide drugs. This, he claimed, eliminates to a great extent the necessity of administering too much alkali, which may be harmful in cases of cardiac or renal disease.

Solution of potassium arsenite and sodium arsenate injected subcutaneously have been of value in the treatment of this disease. I treated a patient in whom dermatitis herpetiformis was controlled with 8 drops daily of solution of potassium arsenite for fifteen years and who had no lesions of this dermatosis while he was receiving neoarsphenamine for an early syphilitic infection. Small doses of the saturated solution of potassium iodide have been employed to desensitize patients with dermatitis herpetiformis.

I have treated 3 patients with dermatitis herpetiformis with anti-histaminic compounds. "Benadryl hydrochloride" N. N. R. (diphenhydramine hydrochloride) and "pyribenzamine hydrochloride" N. N. R. (tripelennamine hydrochloride), 50 mg. four times a day resulted in a favorable reaction in an old woman who was forced to discontinue the use of sulfapyridine because of intolerance to this drug, but treatment with "benadryl" failed in 2 young men who responded promptly to small doses of sulfapyridine. Osborne and his colleagues<sup>41</sup> reported that 3 of the 4 patients they treated with 200 to 300 mg. of "pyribenzamine" daily had almost complete relief of pruritus and burning while taking the drug and the eruption healed. It is possible that success in my cases would have followed the use of larger doses of these drugs.

39. Park, R. G.: Dermatitis Herpetiformis: Failure to Respond to Penicillin, Brit. J. Dermat. 57:151 (July-Aug.) 1945.

40. Lehr, D.: Low Toxicity of Sulfonamide Mixtures: II. Combinations of Sulfathiazole, Sulfadiazine and Sulfamerazine, Proc. Soc. Exper. Biol. & Med. 64: 393 (April) 1947.

41. Osborne, E. D.; Jordan, J. W., and Rausch, N. G.: Clinical Use of New Antihistaminic Compound (Pyribenzamine) in Certain Cutaneous Disorders, Arch. Dermat. & Syph. 55:309 (March) 1947.

count is not uncommon in an acute phase of this dermatosis when the temperature is elevated.

A young man whose eruption of dermatitis herpetiformis was controlled with sulfapyridine observed that this medication was ineffective and that he had a recurrence of pruritus and dermatitis when para-amino-benzoic acid (100 mg. three times a day) was administered. This experience was repeated several times. He also observed that the ingestion of a moderate amount of alcohol each day produced a similar result.

Several patients observed that 1.5 Gm. of sulfapyridine once a day was as effective as 0.5 Gm. three times a day in their keeping free of the eruption.

#### SUMMARY AND CONCLUSIONS

The sulfonamide drugs are of value in the treatment of dermatitis herpetiformis (Duhring). Sulfapyridine is the most effective sulfonamide drug in the treatment of this dermatosis. The average initial daily dose of sulfapyridine for this disease is 1.0 Gm. three times a day, and the average maintenance dose is 0.5 Gm. three times a day.

Twelve per cent of the physicians who had experience with the sulfonamide drugs in the treatment of dermatitis herpetiformis had patients who were cured with this form of treatment. All those who had experience with the sulfonamide drugs in this disease stated that, on the average, 80 per cent of the patients had improved to the extent that they were free of symptoms.

The physical and mental suffering caused by this chronic pruritic vesiculobullous disease warrants the risk of administration of sulfapyridine. Patients should be apprised of the risk involved, in spite of the fact that most of them are willing to assume such risk.

Sulfapyridine has been administered in cases of dermatitis herpetiformis in maintenance doses from three months to seven years with apparent safety. Opinion is equally divided regarding the advantages of continued and interrupted treatment.

Toxic reactions of a mild nature are frequent. Severe toxic reactions are rare if blood cell counts and urinalyses are made at frequent intervals. Copious intake of fluid and alkali therapy reduce the incidence of these reactions.

Herpes gestationis (dermatitis herpetiformis of pregnancy) responds well to the sulfonamide drugs. Dermatitis herpetiformis has been capricious in its response to penicillin. Penicillin is less effective than the sulfonamide drugs. The antihistaminic drugs are probably an adjuvant to the sulfonamide drugs.

About ten days later the family physician called me and stated that she had what he thought was severe erythroderma. I talked to him by telephone and told him what I thought should be done. Two days later I visited her in the hospital. She had a temperature of 103.6 F.; the white blood cell count was 24,000; she was stuporous and her face was swollen and covered with a heavy thick crust. She could hardly open her mouth, and the throat was considerably swollen. The conjunctivas showed bullae. The corneas were cloudy. The skin was bathed with pus and would rub off in large areas. The palms of her hands and feet were denuded of all skin. The finger nails and toe nails were loose. She was seriously ill.

Because of the amount of pus and the seriousness of the infection, she was given penicillin and dextrose solution intravenously, but she died a week later. At autopsy nothing was seen but a small patch of terminal bronchopneumonia.

The question is whether it was dermatitis medicamentosa or true pemphigus foliaceus. The eruption may be attributed to the reaction of the patient to the disease or to the quantity of pathogenic toxins. Certainly there is a close relation between dermatitis herpetiformis and pemphigus foliaceus. I am still undecided. I know that the sulfapyridine had an effect on her, but not whether it produced dermatitis medicamentosa. Dr. Ormsby said that it was a typical picture of pemphigus foliaceus. The odor of pemphigus was distinct in the room.

Since then I have not had the respect for sulfapyridine that I had previously.

DR. SAMUEL AYRES JR., Los Angeles: I think that it is well to bear in mind that possibly this has a multiple causation. There has been a fairly consistent view that a bacterial allergy accounts for some but not necessarily all of the cases of dermatitis herpetiformis.

Probably it is time to decide whether sulfapyridine has virtues over sulfadiazine. It seems to me that sulfadiazine would be the safest drug of this group to use.

It has also been established that these drugs are not overly effective in chronic infections, so that it seems to me questionable procedure to continue their use for an indefinite time, risking sensitization to a valuable drug that might be needed for some other more serious disease.

There is no question that the sulfonamide drugs are of value in many cases of dermatitis herpetiformis. I have had good results using sulfadiazine, however, and I think that it is also of value in some cases of pemphigus, together with eradication of foci of infection. I think that it is necessary to approach the problem from more than one angle and to give sulfadiazine if it seems indicated.

There is also some value in attempting desensitization with either autogenous bacterial vaccine or some nonspecific drug, such as "hapamine" (a chemical combination of histamine and despeciated horse serum globulin), with which I have had excellent results in several cases of dermatitis herpetiformis.

DR. JAMES HERBERT MITCHELL, Chicago: It is not my practice to start treatment with a large dose. I have started with half a tablet (0.25 Gm.), testing the sensitivity, and then have determined the dosage. In my experience that has been the important thing, not the control of the disorder.

I gave one-half tablet to a patient who had had the disorder for many years and who had never been given the drug nor a correct diagnosis. Purpura developed with some minute vesication about the extremities. He recovered from that without any untoward incidents, and ten days later I told him that it should be determined whether or not he was sensitive to the drug and that I should like him to take another dose.

think that it is justifiable to start treatment with small doses and to try to determine the individual tolerance.

DR. JACOB SWARTZ, Boston: Relative to those persons who cannot tolerate sulfapyridine, I have attempted to test the vaccinal reactions to various bacteria and to desensitize with that organism which produces experimentally, at the point of injection, a vesicular reaction. *Bacterium coli* is the organism to which most patients with dermatitis herpetiformis react with vesicular formation.

I have observed this method of treatment, although not as dramatic as sulfapyridine, to be rather helpful in relieving the itching and ultimately to cause the disappearance of the eruption.

Bacterial allergy does not necessarily mean sensitivity to a pathogenic organism. The possibility of sensitization to saprophytes, normally present, must not be overlooked.

DR. MAURICE J. COSTELLO: From the records of patients with dermatitis herpetiformis admitted to dermatologic wards at Bellevue Hospital, it was evident that they suffered from other diseases and that their resistance to infection was poor, especially those infections which involved the respiratory tract. Chronic bronchitis and bronchiectasis were encountered; 2 patients died of pneumonia, and meningococcic meningitis was the cause of death in 1 patient.

In spite of the fact that patients suffering from dermatitis herpetiformis were apprised of the danger of the development of serious toxic reactions following the administration of the sulfonamide drugs, especially sulfapyridine, they stated that they would rather risk it than suffer the intense pruritus and general discomfort associated with this chronic dermatosis.

A study of the temperature charts of the hospitalized patients suffering with this disease in the ten year period 1936-1946 indicated clearly that a low grade elevation of temperature is not uncommon and sudden rises of temperature to 102 or 103 F. occur occasionally.

Several patients obtained equally good therapeutic effect by taking the total maintenance dose of sulfapyridine once a day rather than in divided doses. The general health of the patients was improved. There was increase in weight and strength.

In answer to the question raised by Dr. Mitchell regarding dosage, it has been my aim to give the patient an adequate initial dose and not a large dose of sulfapyridine. Almost invariably the patients in whom toxic reactions developed were those to whom a rather small dose was administered, and the signs of intolerance appeared early.

In spite of the greater frequency of toxic reactions following administration of sulfapyridine, I believe that it is still the drug of choice in the treatment of this inveterate distressingly pruritic dermatosis.

specimens taken from the hand. It is our impression that these cases of psoriasis of the hands are more common than discussions at society meetings or in textbooks would seem to indicate. It is our purpose in this communication to delineate this type of psoriasis of the hands and to

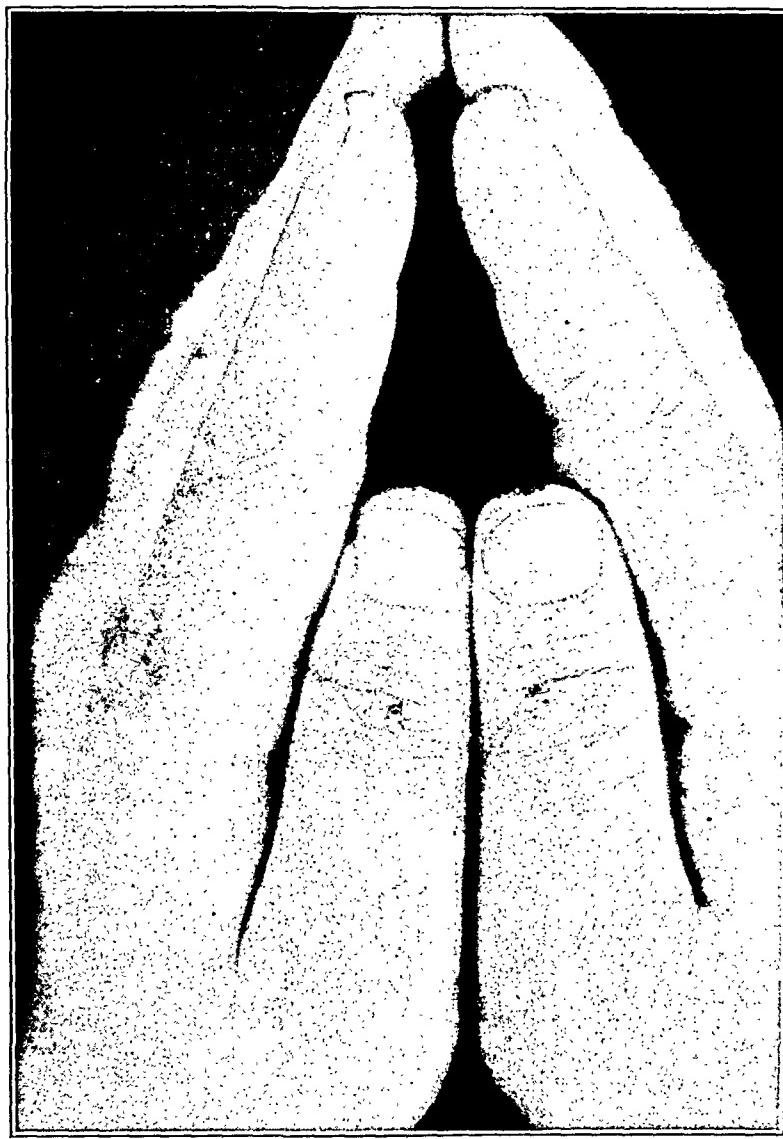


Fig. 1.—Characteristic involvement of the dorsal surfaces of the joints and the lateral aspects of the index fingers.

bring it to more general attention in order that it may be more frequently recognized among the dermatoses of the hands.

The lesions of nonpustular psoriasis of the hands are seen most often on the extensor surfaces of the joints of the fingers (fig. 1) and on the knuckles. They are also frequent on the sides of the fingers and at times

Biopsies in several cases from sites on the palms, sides of the fingers and the joints showed identical histologic features. Sections submitted to dermatopathologists without any information about the cases were diagnosed as psoriasis. The photomicrograph (fig. 3) is so characteristic of the disease that it would be superfluous to describe the histologic observations in these cases.

Nonpustular psoriasis of the hands must be differentiated from chronic dermatophytosis, nummular eczema, chronic dermatitis, neurodermatitis, keratoderma climactericum and syphilis. In the absence of

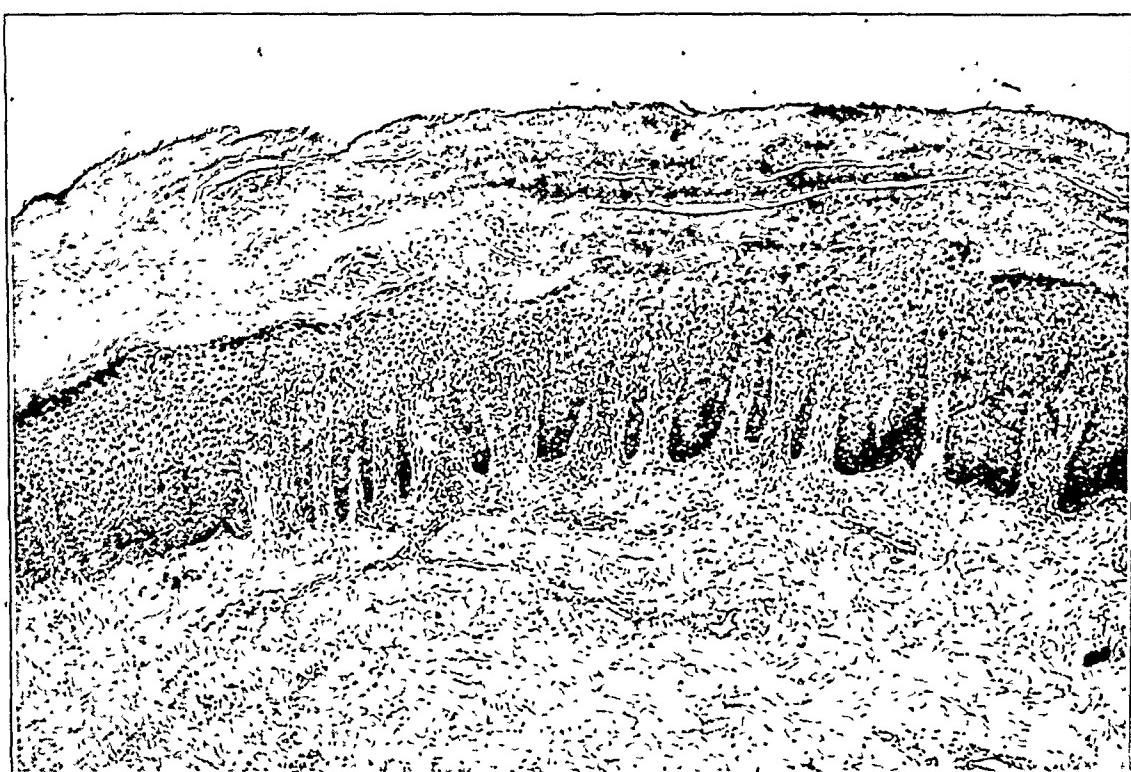


Fig. 3.—Section from a biopsy of a lesion of the finger. The section shows all the histologic features of psoriasis. (Hematoxylin-eosin stain,  $\times 50$ .)

changes in the nails or other typical psoriatic lesions the clinical differential diagnosis may at times be inconclusive. The presence of sharply outlined patches on the extensor surfaces of the joints, sides of the fingers, finger tips or palms, the dell in the patches and the dry scale which becomes silvery on scraping are often helpful in establishing the diagnosis of psoriasis. The final arbiter in most cases, however, is the biopsy, for even in these aberrant lesions the histologic features are diagnostic of psoriasis.

# RELATION BETWEEN THIAMINE AND ARSENICAL TOXICITY

Preliminary Report

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SINCE the introduction of arsphenamine in 1909, the severe reactions of the central nervous system associated with arsenical therapy have been of paramount significance in the treatment of syphilis. Up to 1935, 158 such reactions have been reported in the literature.<sup>1</sup> Of the 158 cases, there were 120 resulting in death, 76 per cent mortality.

Intensive arsenotherapy has been used extensively since 1939, but with constant apprehension because of the increased danger of cerebral complications. Thomas and Wexler<sup>2</sup> stated that the incidence of cerebral symptoms was about 1 per cent in all quick methods of treatment.

The treatment of syphilis with penicillin is still in the experimental stage, and it will be years before the true value of penicillin therapy can be determined. Already a high percentage of relapses have occurred, although toxic reactions are practically nonexistent. It would seem that treatment with penicillin alone does not appear to be equal to the older intensive methods of chemotherapy. It is thus reasonable to assume that arsenicals alone, or accompanying penicillin, may in the future be administered, in spite of the hazards involved in their use. The present trend is toward penicillin therapy in combination with some form of subintensive arsenical therapy.

Many conflicting theories of arsenical encephalopathy are recorded in the literature, the confusion being manifested in the variety of names given to the syndrome: "hemorrhagic encephalitis," "brain purpura," "serous apoplexy," "medullary perivascular necroses" and "pericapillary

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From the Division of Dermatology (Dr. Sexton) and the Department of Pharmacology (Mr. Gowdey), Faculty of Medicine, University of Western Ontario.

1. Glaser, M. A.; Imerman, C. P., and Imerman, S. W.: So-Called Hemorrhagic Encephalitis and Myelitis, Secondary to Intravenous Arsphenamins, Am. J. M. Sc. **189**:64, 1935.

2. Thomas, E. W., and Wexler, G.: Combined Fever and Arsenotherapy, J.A.M.A. **126**:551 (Oct. 28) 1944.

3. Footnote deleted.

encephalorrhagia." The cause of the syndrome has been variously attributed to: (a) the liberation of trivalent inorganic arsenic, due to faulty elimination of the drug by the kidneys and accompanying uremia, (b) a Herxheimer reaction, (c) anaphylaxis and allergy, (d) syphilis itself, (e) injury to the endothelium by a toxin or infectious process, causing hypervasculat dilatation and involvement of the nutrient blood vessels, (f) primary cellular damage of brain tissue with accompanying edema, softening and necroses, (g) hepatic dysfunction and vitamin B<sub>1</sub> deficiency and (h) interference with cellular function by the arsenical combination with the enzyme proteins, physiologically essential groups in the cell, specifically of cellular sulphydryl (SH) groups associated with enzyme proteins.

Of all these theories, the last-mentioned more nearly explains the rapid intoxication which may follow arsenical therapy. Most of the other theories were propounded by pathologists to explain merely the pathologic process. Until recently, successful treatment had not been introduced for this syndrome. However, the introduction of 2,3-dimercaptopropanol (BAL) by Peters, Stocken and Thompson<sup>4</sup> and its subsequent clinical utilization have apparently reduced the mortality rate.

Our interest in this study was stimulated in 1943 by the rapid remarkable recovery of a patient in Victoria Hospital, in whom peripheral neuritis and suspected arsenical encephalopathy had developed during the course of the five day drip treatment and after parenteral administration of massive doses of thiamine hydrochloride. The literature revealed that vitamin B<sub>1</sub> might be a factor in this syndrome, and an extensive survey showed that there was an amazing similarity between the neurology, neuropathology and pathology of arsenical encephalopathy and acute vitamin B<sub>1</sub> deficiency (Wernicke's syndrome, items 1 through 16 in the accompanying table).

Ferraro<sup>5</sup> stressed the organ immunity of sensitivity to a particular toxin, for it determines which organs will be affected in the generalized systemic intoxication. Also, there is a direct relation between the intensity of reaction and the degree of concentration of the toxic substance. Changes in the brain similar to those noticed in arsenical encephalopathy are known to occur in vascular damage, provoked by a variety of dissimilar poisons,<sup>6</sup> for example, carbon monoxide, phosgene

4. Peters, R. A.; Stocken, L. A., and Thompson, R. H. S.: British Anti-Lewisite (BAL), *Nature*, London **156**:616, 1945.

5. Ferraro, A.: Experimental Toxic Encephalopathy, *Psychiatric Quart.* **7**: 267, 1933.

6. Globus, J. H., and Ginsburg, S. W.: Pericapillary Encephalorrhagia Due to Arsphenamine: So-Called Arsphenamine Encephalitis, *Arch. Neurol. & Psychiat.* **30**:1226 (Dec.) 1933. Leifer, W.; Chargin, L., and Hyman, H. T.: Massive Dose of Arsenotherapy of Early Syphilis by Intravenous Drip Method: Recapitulation of Data (1933-1941), *J.A.M.A.* **117**:1154 (Oct. 4) 1941.

and mercury, and by anoxia. All of these poisons produce direct or indirect anoxia. Since the brain is notoriously susceptible to anoxia from any cause and so dependent for energy on efficient carbohydrate

*Neurologic, Neuropathologic and Pathologic Signs and Symptoms of Arsenical Encephalopathy and Vitamin B<sub>1</sub> Deficiency*

Arsenical Encephalopathy	Vitamin B <sub>1</sub> Deficiency
1. Muscular weakness, particularly in extremities; loss of muscular control; pains	Muscular weakness, vague pains, lack of energy
2. Paresthesia in feet and hands	Paresthesia in feet and hands, plantar hyperesthesia, burning of feet
3. Numbness, sensory disturbances, aphasia	"Heaviness" of lower extremities, numbness, loss of vibratory sense, tenderness of calf muscle
4. Absence of patellar and achilles reflexes, hyper-hypoactive; absent and pathologic reflexes occurred in 30% of cases due to arsenicals "606" and "914"	Absence of patellar and achilles reflexes, loss of deep reflexes
5. Stubborn constipation	Decided constipation
6. Partial paraplegia, staggering gait	Staggering gait
7. Babinski's sign	Babinski's sign
8. Regional anesthesia and areas of hyperalgesia	Areas of cutaneous anesthesia, other areas of hyperalgesia
9. Upward spread of paralysis, general body rigidity and opisthotonus or nuchal rigidity occurred in 13% of cases due to arsenicals "606" and "914"	Gradual paralysis, spastic ataxia. Avian opisthotonus is common in quickly occurring acute vitamin B <sub>1</sub> deficiency
10. Weakness of respiratory muscles causes labored breathing (cyanosis occurs)	Edema and pulmonary congestion lead to respiratory failure
11. Mental depression, often psychosis with confusion and disorientation	Psychosis, disorientation, Korsakoff's syndrome
12. Swollen epithelium causes occlusion of blood vessels	Swelling of endothelium with mitotic division of cells, increase in perivascular connective tissues imparting prominence to blood vessels surrounded by the endothelium
13. Degenerative lesions of blood vessels, perivascular hemorrhages, diapedesis, more extensive extravasation, areas of nonhemorrhagic perivascular demyelination which are invaded by scavenger cells	Proliferation of capillaries, minimal amount of leukocytic and lymphocytic perivascular infiltration
14. Dilatation of capillaries, hemorrhages in cord, cerebral cortex, cerebral edema, petechial hemorrhages	Pseudoencephalitic hemorrhagic changes in brain, dilatation of capillaries, edema
15. Complete destruction of all ganglion cells and anterior horn lymphocytes, polymorphonuclear infiltration	Disintegration of ganglion cells replaced by astrocytes, microglia and fibroblasts. Monocellular phagocytes filled with fat and other debris are conspicuous at one stage
16. Focal vascular lesions which permit escape of blood into perivascular tissues, sometimes even perivascular necrosis of demyelination, usually groups of lesions in symmetric situations, occasionally grouping together of lesions to form gross cerebral hemorrhages. Multiple symmetric foci of red softening, involving both gray and white matter of the brain or combinations of these various groups of lesions often occur	Besides the degeneration of the myelin sheaths of peripheral nerves, there is vascular degeneration of the cells of Schwann and later fragmentation of the axis-cylinders. Less certain are the degenerative changes of ganglion cells of the brain, cerebellum, spinal cord and dorsal root ganglions. Wencheback described a hydropic degeneration of cardiac muscle cells as a typical microscopic lesion in beriberi
17. Zones of predilection: corpus callosum, optic thalamus, caudate nuclei, external capsule and brain stem. Necrosis of the intervening tissue causes softening	Lesions occur in certain zones of predilection: periventricular gray matter around the third ventricle, mammillary bodies, periaqueductal region, corpora quadrigemina, and cranial nerve nuclei beneath the ependyma of the fourth ventricle

metabolism, it is not impossible that this cerebral syndrome may be caused by enzymatic dysfunction. The work of Peters, Stocken and Thompson<sup>4</sup> revealing the arsenical combination with the protein enzyme action of the tissue cell structure, thus interfering with function, might

Somogyi<sup>12</sup> was employed for the determination of the level of blood sugar.

Preliminary investigation included a detailed history of diet. The patient was questioned closely to determine whether he had ever had muscular cramp, burning of the feet, anorexia, constipation and the like. A great deal of stress has been placed on the increased muscular sensitivity, loss of vibratory senses and altered reflexes in the diagnosis of subacute vitamin B<sub>1</sub> deficiency. In our study, we combined a new quantitative method of measuring the muscular sensitivity (appendix A) with the estimation of pyruvic acid, lactic acid and sugar in the blood to determine whether patients, on entering the hospital, were inclined to be deficient in vitamin B<sub>1</sub>. Daily biochemical and muscular sensitivity tests were made, beginning on the day before and continuing through the period of drip treatment. When a reaction occurred the biochemical tests were made more frequently.

Thirteen cases were studied in which intensive five day drip arsenical therapy was given, as indicated previously. The eleventh, or fatal case, is recorded first, for the purpose of comparison, followed by 2 cases of acute arsenical intoxication with recovery. Studies of animals revealed 2 similar cases of intoxication, which are reported in detail.

#### REPORT OF CASES

**CASE 1.—Biochemical and Clinical Manifestations of a Fatal Case of Arsenical Encephalopathy and the Effect of Large Doses of Thiamine During the Course of the Reaction.**—Miss E. W., aged 20, was admitted to the hospital Oct. 20, 1945, with secondary syphilis, a positive reaction in serologic tests of the blood, 80 quantitative Kahn units, and condylomas. Physical examination revealed nothing unusual. Studies of the chemical composition of the blood revealed: nonprotein nitrogen 32.6 mg. per hundred cubic centimeters, sugar 101 mg., hemoglobin 70 per cent, red cells 3,380,000, color index 93, leukocytes 4,750, neutrophils 70 per cent (mature forms 62 and young forms 8 per cent), lymphocytes 28 per cent and eosinophils 2 per cent. The differential blood cell count showed secondary anemia, which was not consistent with secondary syphilis. The coagulation time was six and one-half minutes, and the bleeding time was two and one-half minutes. The icteric index was 3.5 units.

Previous to arsenotherapy, this patient received 600,000 units of penicillin. A total of 0.76 Gm. of oxphenarsine hydrochloride was administered in drip therapy. Routine investigation revealed a mild subacute vitamin B<sub>1</sub> deficiency in the dietary history. The level of pyruvic acid in the blood was 230 per cent of normal, the lactic acid was normal, the blood sugar was 60 mg. and reactions to muscular sensitivity tests were slightly increased above normal.

The course during the five-day oxphenarsine hydrochloride drip was uneventful, until the afternoon of the third day, when the temperature rose to 102 F. Muscular sensitivity was increased 65 per cent over the patient's normal level. The drip therapy was discontinued immediately. Metabolic tests were not obtained at this

12. Somogyi, M.: A Method for the Preparation of Blood Filtrates for the Determination of Sugar, J. Biol. Chem. 86:655, 1930.

juncture. Muscular sensitivity reactions were increased to twice the normal. On the fourth day the temperature had returned to normal. Drip therapy was resumed. In midafternoon, the temperature rose to 100.3 F. The metabolic rate and sensitivity reactions were unchanged, but continued well above the normal as on the first day. On the fifth day, drip therapy was again started, the temperature being initially 99.0 F., which rose in the afternoon to 101.3 F., gradually decreasing to 99.1 F. by morning. Again the muscular sensitivity reactions and metabolic rate were unaltered from those of the previous day. On the sixth day drip therapy was again started, the temperature being 99.1 F. At noon the levels were: pyruvic acid 245 per cent of normal, lactic acid within normal limits and blood sugar normal, and the temperature was 99.3 F. The patient complained of headache. The drip

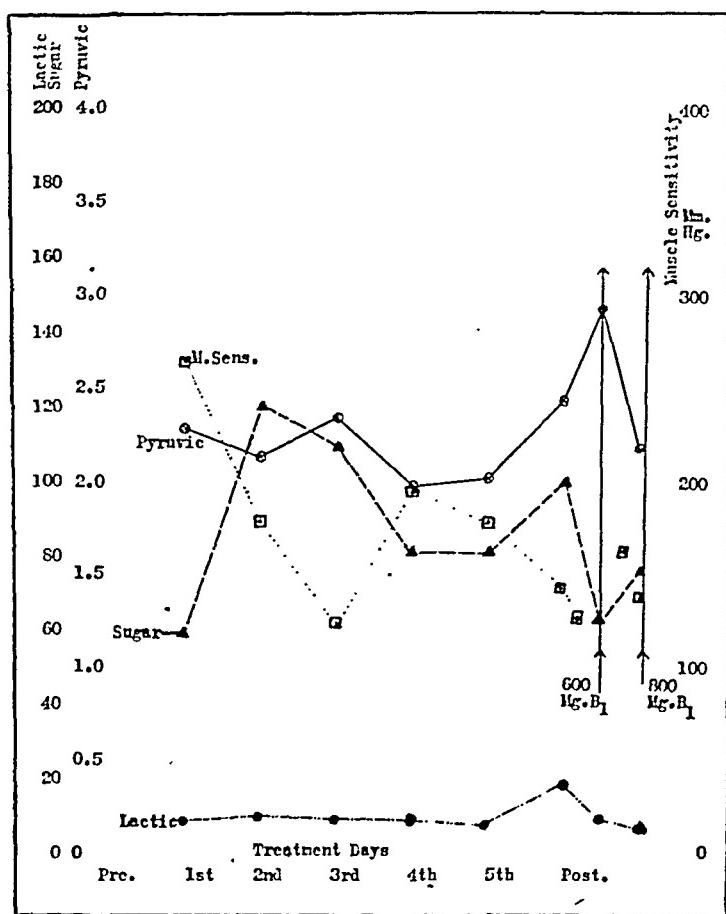


Fig. 1 (fatal clinical case).—Graph depicting initial high and gradually increasing level of pyruvic acid in conjunction with increasing muscular sensitivity and transient improvement after vitamin B<sub>1</sub> therapy.

therapy was discontinued when the patient became drowsy. Six hundred milligrams of vitamin B<sub>1</sub> were administered, with an improvement in the level of pyruvic acid and muscular sensitivity reactions. Twenty cubic centimeters of spinal fluid were withdrawn, with no variation from the normal. Cutaneous sensitivity was extreme, the slightest touch causing pain. The patient became drowsy, and at midnight the blood pressure was 100 systolic and 60 diastolic. Eight hundred milligrams of vitamin B<sub>1</sub> were given, after which there was temporary improvement; but on the morning of the seventh day she was dazed, responding slowly to questioning. Although treatment with vitamin B<sub>1</sub> was continued little change

was noted from this point. During the afternoon the patient was dazed and drowsy and had convulsions, which were controlled with pentothal sodium. The patient became progressively worse, in spite of spinal fluid drainage and administration of epinephrine, oxygen and hypertonic dextrose solution. The patient lingered for two days, completely comatose, spastic and incontinent, with her temperature slowly rising to shock level and her blood pressure falling with fast thready pulse. The patient died within two days after drip therapy was discontinued.

*Postmortem Observations.*—The diagnosis was typical hemorrhagic encephalitis (characteristic of so-called arsphenamine encephalitis). Gross cerebral lesions of the brain were described as: (1) multiple punctate petechial hemorrhages in both white and gray matter, prominently in the gray matter (cortex) and centrum of the temporal lobes and symmetrically distributed there, but also in the claustrum, in the external capsule, extending downward into the hippocampal gyri, and in the hypothalamic region and (2) multiple symmetric foci of hemorrhagic necroses, occurring chiefly in the claustrum, external capsule, hippocampal gyri, corpus callosum and left internal capsule. An area of softening and liquefaction was present in the white matter in the anterior pole of the right temporal lobe.

*Bacteriologic Study of the Spinal Cord:* There were no definite lesions within sections of the spinal cord taken from different levels. However, the anterior nerve roots appeared slightly shrunken and did seem to show slight demyelination and some fragmentation of the myelin sheaths. No degeneration of anterior horn cells was detected. Unfortunately, no peripheral nerves were sectioned, so it was difficult to give a definite opinion as to whether or not peripheral neuritis was present.

*Comment.*—Pretreatment examination of this patient revealed a suggestive history of avitaminosis. The abnormal ratio of lactate to pyruvate acid was confirmative, as were the increased muscular sensitivity reactions. On the basis of this information, we feel that intensive arsenical therapy was hazardous, that the patient should have been protected with large doses of vitamin B<sub>1</sub> and that the treatment should have been commenced with more than the usual care and apprehension or not at all.

By the time vitamin B<sub>1</sub> was administered an advanced stage of so-called hemorrhagic encephalitis had been reached. In other words, her disease had proceeded from a biologic lesion to an irreversible pathologic one.

The rise of temperature on the third day to 102 F. was accompanied with a "telltale" fluctuation in the level of pyruvic acid and in muscular sensitivity, and undoubtedly permanent cessation of treatment or immediate administration of maximum doses of vitamin B<sub>1</sub> was indicated at this stage. These elevated levels continued until noon of the sixth day when the onset of acute symptoms was heralded by a sharp rise in pyruvic acid to 245 per cent of normal, with a normal level of lactic acid and increased muscular sensitivity, as well as tenderness of the peripheral nerves.

It was not until the clinical stage, consisting of headache, drowsiness and disorientation was reached, that vitamin B<sub>1</sub> was administered. This, of course, proved to be futile.

*CASE 2.—Biochemical and Clinical Manifestations of Arsenical Intoxication and the Effect of Thiamine.*—The patient was a 23 year old man, whose history suggested possible deficiency in vitamin B<sub>1</sub>. Frequent vomiting, anorexia and constipation were reported, along with the fact that the patient often had muscular cramp after exercise and hyperesthesia. Although the vibratory sense and reflexes showed

but three hours later it had again increased. Another 500 mg. was given, at which time the pyruvic acid had decreased to 260 per cent of normal, and the blood sugar had dropped to 190 mm. per hundred cubic centimeters. The response of the patient was spectacular; he became less lethargic and more cooperative, and the headache disappeared. The next morning the patient was bright and cheerful and "felt much better." A test of the fragility of the red blood cells made that morning showed that hemolysis began at 0.38 per cent and was complete at 0.28 per cent (normal, 0.42 to 0.32). Acetone end bodies in the urine, with the accompanying weak spells and diaphoresis, remained for about a week (fig. 1).

*Comment.*—This patient's symptoms are hard to evaluate. He had an extremely sensitive nervous system for years, and he complained of headaches. In general, the opinion was that his complaints were accentuated. During drip treatment, which he viewed with apprehension, he had severe infective phlebitis of both arms from the needle, which might easily account for many of his constitutional symptoms, such as fever, headache, backache and even petechial hemorrhages of the abdomen. However, his clinical manifestations and biochemical abnormalities did parallel those of the proved hemorrhagic encephalitis in case 1. The remarkable clinical improvement, as well as the biochemical improvement, after massive doses of vitamin B<sub>1</sub>, lends added weight to the assumption that he was suffering from hemorrhagic encephalitis. An examination of spinal fluid was not made, but the examination of the spinal fluid in the fatal case (case 1) had not been enlightening.

**CASE 3.—Biochemical and Clinical Observations.**—The patient was a woman aged 24. Preliminary examination six weeks post partum indicated that she was deficient in vitamin B<sub>1</sub>. The diet had been poor. Her vibratory sense and reflexes suggested a low level of thiamine. The pyruvic acid in the blood was twice the normal level. This was especially significant, since the previously recorded level of lactic acid had been normal. The blood sugar was high and variable, indicating again subacute B<sub>1</sub> avitaminosis.

On the day preceding the arsenical treatment, the blood sugar was 350 mg. per hundred cubic centimeters, at which time the muscular sensitivity was 100 mm. of mercury. This showed extreme sensitivity, compared to a normal level of 300 mm. Six hundred milligrams of vitamin B<sub>1</sub> were given intravenously. Two hours later the muscular sensitivity had decreased two and one-half times. Evidence of tissue saturation by vitamin B<sub>1</sub> was shown by the fact that the level of pyruvic acid was down to normal. The level of lactic acid was normal, and the blood sugar had dropped to 85 mg. per hundred cubic centimeters.

During the five day drip treatment with oxophenarsine hydrochloride the level of pyruvic acid was somewhat above normal, and yet at no time did the patient show evidence of arsenical intoxication, nor did a muscular sensitivity test indicate that the arsenic had created B<sub>1</sub> avitaminosis. This was confirmed by the fact that the blood sugar remained within the normal limits.

#### BIOCHEMICAL AND CLINICAL OBSERVATION OF NINE PATIENTS

Nine patients, none of whom had vitamin B<sub>1</sub> deficiency or other serious clinical symptoms, showed a decided upset in carbohydrate metabolism during the five day oxophenarsine hydrochloride drip therapy. The level of pyruvic acid rose early in the treatment and remained above normal until after the drip was completed. In general, a high level of pyruvic acid synchronized with clinical upset and was associated with increased muscular sensitivity. Levels of lactic acid

remained normal throughout the treatment. By far the most variable factor was the level of blood sugar (the drip contained 5 per cent dextrose), which rose on the first day. Moderate hyperglycemia was consistently present throughout the period of treatment.

#### STUDIES OF ANIMALS

Experiments were carried out with dogs to determine whether a normal dog would show evidence of an upset in carbohydrate metabolism, more specifically a vitamin B<sub>1</sub> deficiency, when given the five day oxophenarsine hydrochloride drip. The procedure was conducted as described by Shaffer.<sup>12a</sup> Whereas the regular drip requires twelve hours and 35 cc. of 5 per cent dextrose per kilogram, this drip required one hour and 15 cc. per kilogram. No anesthetics or hypnotics were given in order to avoid complicating factors. Veins in the leg were used for obtaining samples of blood and administration of the drip. The oxophenarsine hydrochloride dose was regulated on a milligram and kilogram basis, comparable to human dosage.

The results paralleled the clinical studies, namely, a significant derangement in carbohydrate metabolism as evinced by increased pyruvic acid and sugar in the blood during the course of the drip.

The following toxic reactions in 2 dogs, described in detail, are enlightening. It is hoped that the observations may be fully substantiated in subsequent studies.

Dog 1.—This was a black mongrel female hound, weighing 12.8 Kg., that was primarily deficient in thiamine, as shown by an excessively high level of pyruvic acid. The five-day drip was given, consisting of 0.04 Gm. of oxophenarsine hydrochloride in 150 cc. of 5 per cent dextrose. The level of pyruvic acid gradually rose throughout the treatment, with the blood sugar gradually decreasing, because the dog would not eat after the second day of treatment. At the end of treatment each day the dog vomited. On the fourth day the temperature rose, the hearing was dulled, and the dog was weak. On the fifth day the level of pyruvic acid level was 260 per cent of normal, lactic acid 200 per cent of normal and blood sugar 50 per cent of normal. The dog became cold and anoxic while on the table, could scarcely hear and was too weak to walk. On the eighth day the dog died. The postmortem examination showed the typical pathologic changes of arsenical encephalopathy (appendix B).

Dog 2.—This was a male mongrel collie, weighing 14.1 Kg. Two separate experiments were performed: (1) the five-day oxophenarsine hydrochloride rapid drip followed by a glucose tolerance test and (2) the five-day exophenarsine hydrochloride rapid drip, with thiamine given every day immediately after the drip and then a glucose tolerance test. The five-day drip consisted of 150 cc. of 5 per cent dextrose and 0.04 Gm. of oxophenarsine hydrochloride each day. The level of pyruvic acid (200 per cent of normal) gradually rose to 300 per cent of normal on the

12a. Shaffer, L. W.: Present Status of the Intensive Arsenotherapy of Early Syphilis, *Ven. Dis. Inform.* **24**:108, 1943.

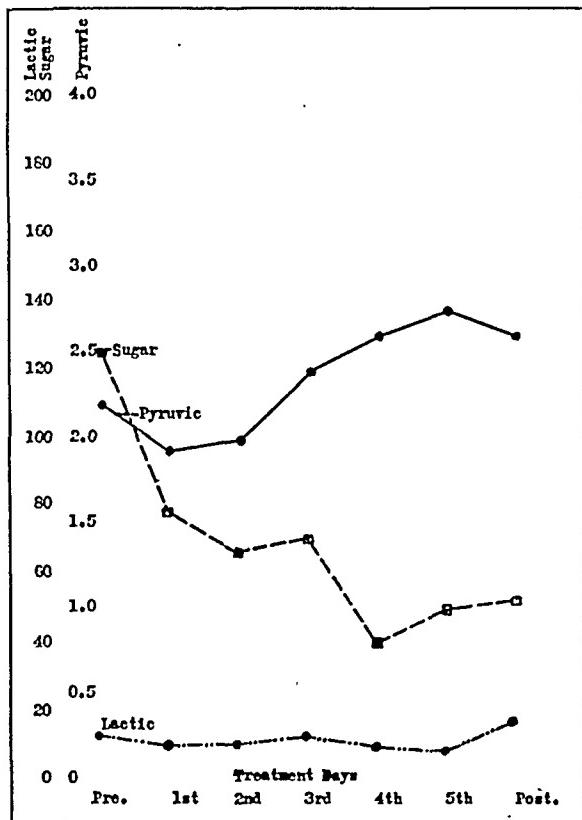


Fig. 3 (dog 1, fatal case).—Graph showing increased level of pyruvic acid with contrasting normal level of lactic acid during five day drip.

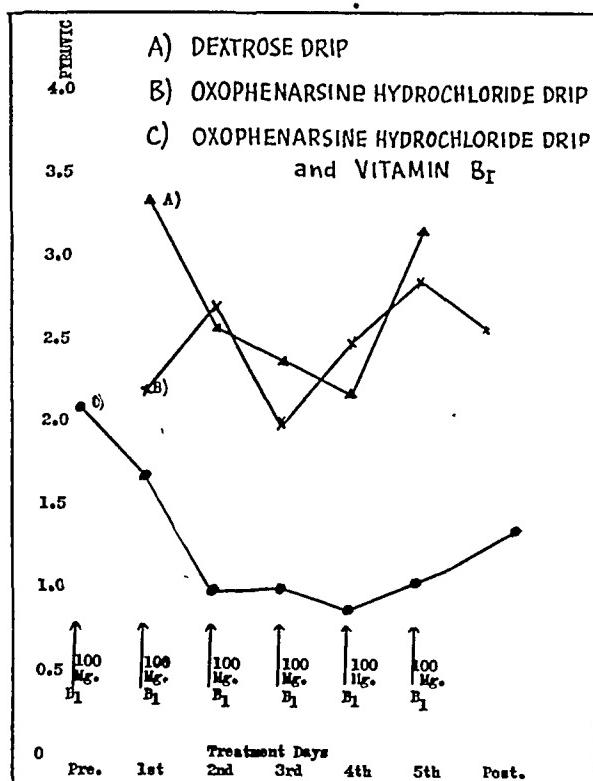


Fig. 4 (dog 2).—B, elevated level of pyruvic acid with oxophenarsine hydrochloride drip alone. C, normal level of pyruvic acid when the animal was protected with vitamin B<sub>1</sub>.

fifth day. Levels of blood sugar and lactic acid were normal throughout. No toxic symptoms were observed. The day following the drip, the pyruvic acid had decreased. The reaction to a glucose tolerance test was normal.

Five months intervened between the two five-day oxophenarsine hydrochloride drips. The reaction to a glucose tolerance test on the day preceding the drip was normal. The pretreatment level of pyruvic acid was above normal (2.1 mg. per hundred cubic centimeters). One hundred milligrams of vitamin B<sub>1</sub>, administered intravenously, lowered the level of pyruvic acid to 1.7 mg. per hundred cubic centimeters on the first day of the drip. Two hundred and sixty milligrams of oxophenarsine hydrochloride were administered over the five day period. Immediately after the drip had been stopped each day, 100 mg. of vitamin B<sub>1</sub> were given intramuscularly. This route of injection was used to insure an adequate level of thiamine at the precise time that most of the arsenic was being withdrawn by the tissues. It was hoped that thiamine, given prophylactically, would prevent serious disorders in carbohydrate metabolism.

This time, the level of pyruvic acid remained normal throughout the period of treatment, as did the lactic acid and sugar. No derangement in metabolism occurred. Results for the follow-up glucose tolerance test were normal.

#### COMMENT

In the 2 cases with fatal results (case 1 and dog 1) there were high initial levels of pyruvic acid. These high levels of pyruvic acid continued throughout the treatment and gradually increased. Our present knowledge indicates that in case 1 we should have stopped the clinical drip on the third day when the already high level of pyruvic acid rose, the muscular sensitivity greatly increased and the patient had a systemic reaction. Intravenous administration of 2,3-dimercapto-propanol (BAL) at that time would most probably have reversed the biochemical dysfunction and certainly would have inactivated further toxicity of the enzyme system; but the correlation between the high level of pyruvic acid and clinical intoxication was not sufficient to justify our discontinuing arsenotherapy. If the drip had been stopped, vitamin B<sub>1</sub> had been given and the patient had recovered, then the fact that early encephalopathic changes had occurred would have been disputed.

Peters<sup>13</sup> maintained that nervous symptoms of acute vitamin B<sub>1</sub> deficiency are not caused by any toxic effect of accumulated lactate, pyruvate or any other metabolite, but by a biochemical lesion brought about by ". . . the absence of an important factor in the development of energy from carbohydrates. . . ." Wortis and his associates<sup>14</sup> stated that in clinical vitamin B<sub>1</sub> deficiency there is first an altered function in the cells, then a biochemical lesion and then a definite pathologic lesion. The extreme importance of the time element is

13. Peters, R. A.: The Biochemical Lesion in Vitamin B<sub>1</sub> Deficiency, *Lancet* **1**:1161, 1936.

14. Wortis, H.; Bueding, E.; Stein, M. H., and Jolliffe, N.: Pyruvic Acid Studies in the Wernicke Syndrome, *Arch. Neurol. & Psychiat.* **47**:215 (Feb.) 1942.

emphasized in the described case of arsenical encephalopathy. Large doses of thiamine were given, and although the patient did respond at first (shown in the decrease in the levels of pyruvic acid and lactic acid) the end result suggested that by the time the thiamine was administered the biochemical lesion had become an irreversible pathologic one. At this stage BAL, if it had been available, would have been of little value for the same reason, which probably explains the failures (15 per cent) reported by Eagle and Magnuson<sup>15</sup> in their series of patients treated with BAL. The drug inactivates the arsenical and reverses the toxic action, provided that the action has not been too prolonged.<sup>4</sup> Its use is limited after toxicity has occurred. As described previously, vitamin B<sub>1</sub> deficiency can be an indication of impending toxicity, and the vitamin may be used in supportive treatment with BAL to prevent toxicity. The latter supposition is being further studied by experimentation with animals.

#### SUMMARY AND CONCLUSIONS

These experiments show that oxophenarsine hydrochloride does cause a significant derangement in carbohydrate metabolism, as evinced by increased pyruvic acid and sugar in the blood. The greater the clinical toxicity, the greater is the upset of carbohydrate metabolism. The high level of pyruvic acid suggests that catabolism is stopped at the level of pyruvic acid. This is directly related to the functioning level of thiamine, since a deficiency of the coenzyme containing thiamine produces a high level of pyruvic acid.

A sudden rise in the level of pyruvic acid, coinciding with greatly increased muscular sensitivity and rising temperature, is experimental evidence of a reaction of severe toxicity. In a reaction seriously involving the central nervous system, if vitamin B<sub>1</sub> and 2,3-dimercaptopropanol (BAL) are to be used therapeutically, they must be given early, before the reaction has gone beyond the irreversible pathologic lesion.

Five cases of acute arsenical intoxication are described. In all 5, the level of pyruvic acid was high throughout the course of the drip and the curves portraying this high level of pyruvic acid were all of the same general shape. It would seem that BAL and vitamin B<sub>1</sub>, in adequate dosage, should be complementary in the treatment of arsenical encephalopathy. Administration of vitamin B<sub>1</sub> insures the functioning at peak levels of the cell enzyme systems not affected by the arsenical. When the usefulness of vitamin B<sub>1</sub> has been exceeded, then BAL may be used to inactivate the arsenical, though, of course,

15. Eagle, H., and Magnuson, H. J.: The Systemic Treatment of Two Hundred Twenty-Seven Cases of Arsenic Poisoning (Encephalitis, Dermatitis, Blood Dyscrasias, Jaundice, Fever) with 2, 3-Dimercaptoproponal (BAL), Am. J. Syph., Gonor. & Ven. Dis. 30:420, 1946.

this means the loss of its spirocheticidal effect. Lastly, an initial pretreatment high level of pyruvic acid accompanied with clinical signs of subacute B<sub>1</sub> avitaminosis should warrant treatment other than intensive arsenotherapy.

APPENDIX A.—Dr. Grant Skinner, formerly of the Department of Pharmacology, who gave invaluable assistance in the early stages of this study, originated the following quantitative method for estimating muscular sensitivity.

Clinicians have consistently reported increased muscular sensitivity in vitamin B<sub>1</sub> deficiency and, indeed, have long used that fact in making such a diagnosis. The apparatus is a mercury manometer, attached to an ordinary blood pressure cuff, which can be pumped to a pressure of 500 mm. of mercury. The cuff is placed around the arm or calf muscle, and it is pumped quickly (to prevent ischemia) until the patient feels a definite cramping pain in the muscle. The manometer reading is simultaneously recorded.

Tests on 40 normal women have shown that the average normal reading for women is 400 mm. of mercury for the arms and 300 mm. for the legs. The normal for men, deduced by running tests on 40 normal subjects, shows that their level is somewhat higher, viz., 470 mm. of mercury for the arms and 400 mm. for the legs.

Tests performed on subjects suspected of B<sub>1</sub> avitaminosis showed that the pressure that they can bear without pain is greatly reduced, running from leg values of 250 mm. of mercury down to 100 mm., depending on the degree of deficiency. That this increased sensitivity is due to lack of thiamine has been proved by administering large doses of vitamin B<sub>1</sub> intravenously. A prompt and lasting rise in the pressure level, showing a decreased muscular sensitivity, consistently occurs.

APPENDIX B.—Pathology of Hemorrhagic Encephalopathy in a Dog: The postmortem examination showed a fiery red small intestine, with hyperemia and greatly engorged vessels. The brain showed considerable edema and multiple petechial hemorrhages. The capillary vessels were enlarged. Hemorrhages were present all over the brain, many in the hemispheres, pons and thalamus. They were also present in the region of the corpora quadrigemina, sulcus basilaris and the genu of the corpus callosum. Those in the midbrain and isthmus rhombencephali were much worse than in the forebrain and hindbrain. They were present even in the cerebellum and medulla oblongata. A cross section through the diencephalon showed hemorrhages throughout, which were worse near the margin.

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## MYOBLASTOMA

Report of a Case of Myoblastoma of the Lip Followed by Multiple Tumors of the Skin

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THE LITERATURE dealing with the subject of myoblastoma is found almost exclusively in journals of surgery and pathology. As far as we could determine, there is only one article by Tuta and Schmidt,<sup>1</sup> in addition to a specimen presentation by Schmidt<sup>2</sup> and a case presentation by Ebert and Slepian,<sup>3</sup> published in the ARCHIVES OF DERMATOLOGY AND SYPHILOLOGY. This paucity in dermatologic literature is surprising, when one considers that the percentage of cases of myoblastoma located in the skin and subcutis amounts to 20.4 per cent (Powell<sup>4</sup>), second in order of frequency to location on the tongue, which is seen in 37.6 per cent of the cases. We believe that a better acquaintance of dermatologists with this type of tumor will probably reveal a still higher incidence of myoblastoma in the skin. Until now a number of these tumors were diagnosed as xanthoma, which they resemble microscopically. Thus, the case presented by Moschcowitz<sup>5</sup> in 1922 as xanthelasma of the tongue was later observed to be myoblastoma. The case of myoblastoma of the gingiva in a newborn infant reported by Battaglia and Curphey<sup>6</sup> and 2 cases of Howe and Warren<sup>7</sup>

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1. Tuta, J. A., and Schmidt, F. R.: So-Called Myoblastoma, Arch. Dermat. & Syph. **46**:225 (Aug.) 1942.
2. Schmidt, F. R.: So-Called Myoblastoma of the Skin, Arch. Dermat. & Syph. **45**:1209 (June) 1942.
3. Ebert, M. H., and Slepian, A. H.: So-Called Myoblastoma, Arch. Dermat. & Syph. **48**:348 (Sept.) 1943.
4. Powell, E. B.: Granular Cell Myoblastoma, Arch. Path. **42**:517 (Nov.) 1946.
5. Moschcowitz E.: Xanthelasma of the Tongue, Proc. New York Path. Soc. **22**:135 (Oct.-Dec.) 1922.
6. Battaglia, J., and Curphey, T. J.: Gingival Tumor of Newborn, Am. J. Dis. Child. **57**:1404 (June) 1939.
7. Howe, C. W., and Warren, S.: Myoblastoma, Surgery **16**:319 (Sept.) 1944.

striations were described by Klemperer<sup>12</sup> and by Crane and Tremblay,<sup>9</sup> but their occurrence is rare. The cytoplasm has a tendency to eosinophilia. According to Horn and Stout<sup>13</sup> there is great variation in the number, size and density of the granules and in the depth of acidophilic staining. The nuclei are centrally located, fairly regular, small and dense, and there are rarely mitoses present. Some cells may be multi-nucleated. Fine strands of connective tissue support single cells or groups of cells. The majority of these tumors are well delimited, but a few are truly encapsulated.

#### MALIGNANCY

While myoblastoma may be considered as a benign tumor, there are several reports of its malignant behavior. Some of these, like the cases of Howe and Warren,<sup>7</sup> probably belong to group 4 of Abrikosoff's classification, which according to Ravich, Stout and Ravich<sup>14</sup> should be separated altogether from the group of myoblastomas, as they probably represent polymorphous sarcomas. According to these authors, in most of the literature subsequent to the work of Abrikosoff, the term myoblastoma is used for such cases of sarcoma. These authors expressed the opinion that tumors belonging to the first three groups of myoblastoma in Abrikosoff's classification, since they are almost all benign, should be labeled with a distinctive name. Thus they would not be confused with the other forms of striated muscle tumors, most of which are malignant. They chose, therefore, the term "granular cell myoblastoma."

There are, however, definite cases of myoblastoma reported which show malignant behavior. Here belong the case of Morpurgo<sup>15</sup> of a tumor of the tongue, with metastases in the cervical lymph nodes, resulting in death, the fatal case of Ravich, Stout and Ravich<sup>14</sup> of myoblastoma of the urinary bladder, with metastases in the lumbar vertebra, liver, spleen and lymph nodes, and case 3 of Powell<sup>4</sup> of myoblastoma of the tongue, which resulted in death through local invasion of the tumor and erosion of a blood vessel.

#### NATURE AND ORIGIN OF MYOBLASTOMA

There is no agreement as to the origin of these tumors. Gray and Gruenfeld<sup>16</sup> expressed the opinion that not all myoblastomas are

13. Horn, R. C., and Stout, A. P.: Granular Cell Myoblastoma, Surg., Gynec. & Obst. **76**:315 (March) 1943.

14. Ravich, A.; Stout, A. P., and Ravich, R. A.: Malignant Granular Cell Myoblastoma Involving the Urinary Bladder, Ann. Surg. **121**:361 (March) 1945.

15. Morpurgo, B.: Myoblastomi, Arch. per le sc. med. **59**:229 (Feb.) 1935.

16. Gray, S. H., and Gruenfeld, G. E.: Myoblastoma, Am. J. Cancer **30**:699 (Aug.) 1937.

histogenetically identical. They distinguished between the tumors located in areas where striated muscle is present, as in the tongue and in skeletal muscles, and those located elsewhere where normally there is no striated muscle. Thus, they considered lingual tumors as due to necrobiosis of muscle fibers, while the exact nature of the latter type of tumors they left open to question. According to Tuta and Schmidt<sup>1</sup> the characteristic granular cells seen in myoblastomas located in striated muscle and in other locations are identical, although they did not believe in their myogenous origin. They considered these cells distinct from those with striations, which are seen in tumors located in muscle tissue and which they considered as degenerated adult muscle fibers. Klemperer,<sup>12</sup> however, stated that granular cells strongly suggest identity with ancestral cells of the striated muscle. And this seems to be the opinion of most authors, who favor the dysontogenetic theory of Klinge.<sup>17</sup> This theory maintains that the tumors arise from retained or misplaced primitive myoblasts which failed to develop into adult muscle tissue.

#### REPORT OF A CASE

M. D., a Negro woman, aged 35, registered on March 16, 1945 at the Sydenham Hospital Skin Clinic, complaining of a growth on the lip which had been present for more than two years and which hardly changed in size in the previous one and one-half years. On examination, there was seen on the inner aspect of the lower lip near the left angle of the mouth, a hazelnut-sized round raised tumor with a pinkish rough surface. Palpation revealed the tumor to be hard and extending deep into the submucosa. There was no regional adenopathy. Routine medical and laboratory examination of the patient revealed nothing abnormal, except for a Wassermann reaction of the blood of 1 plus. There was a history of three miscarriages at four and one-half, four and three months of pregnancy, respectively, but the patient denied knowledge of any syphilitic infection or any previous antisyphilitic treatment. Because of the location of the lesion the diagnosis of epithelium was considered, although the diagnosis of a benign tumor was favored.

A biopsy was performed, and endothermy was used to destroy the rest of the lesion. However, a small flat cartilaginous-like hard piece at the lateral edge of the tumor was left embedded in the submucosa as it resisted the endothermy spark and offered great difficulty in excision by knife.

The pathologic observations were as follows: The specimen was from the lip, measuring approximately 4 mm. in thickness. On section the tissue was firm, thickened and whitish.

Microscopic sections showed typical myoblastoma. The tumor occupied the lamina propria, extending directly up to the overlying epithelium. The tumor was well localized, but neither sharply demarcated nor encapsulated. It did not completely replace the lamina propria, of which isolated collagen fibers remained amidst the tumor cells. The latter were otherwise fairly compact and uniform. They were large cells, about 20 microns in diameter, rounded or polyhedral, with a large proportion of cytoplasm and relatively small nuclei. The cytoplasm had a distinctively granular structure. The granules were coarse, slightly eosinophilic

17. Klinge, F.: Ueber die sogenannten unreifen, nicht quergestreiften Myoblastenmyome, Verhandl. d. deutsch. path. Gesellsch. 23:376, 1928.

and, in most of the cells, more or less densely packed. In a small proportion of the cells the cytoplasm had a somewhat foamy or vacuolated appearance, suggestive of xanthoma cells. However, frozen sections stained with Sudan IV indicated entire absence of fat from the tumor cells. Detailed study of the tumor cells revealed no evidence of ribbon or syncytial elements, striations or transitions between tumor cells and normal muscle cells.



Fig. 1.—Section of the tumor of the lip, showing considerable proliferation and pearl formation in the overlying epithelium and the myoblastoma cells in the papillary layer of the corium extending directly up to beneath the epidermis ( $\times$  approximately 675).

The overlying epithelium showed considerable change. There was moderate hyperkeratosis and parakeratosis and decided acanthosis with proliferation and extension of the epithelial pegs deep into the underlying stroma. A number of proliferated cell nests showed distinct pearl formation, but there was relatively little cell atypia and few mitoses were present (fig 1).

thigh above the knee; there was a similar lesion on the lateral aspect of the trunk in the left lumbar region, and a similar but smaller lesion was situated on the right hip. These tumors had been noticed by the patient one year previously. On the lower lip, in the area of the tumor from which a biopsy had been pre-



Fig. 3.—Section from the inferior portion of the cutaneous tumor, showing infiltration at the border of the tumor into the underlying subcutaneous fat tissue ( $\times$  approximately 85).

viously made and which had been treated, the small hard platelike lesion was present, unchanged since the time of the last examination two years previously. These lesions suggested noduli cutanei, but because of the previous history and

the observations at biopsy of the tumor of the lip, a microscopic examination of these newly developed tumors was thought to be of importance.

The three nodules were excised and examined microscopically, with the following observations. There were three specimens of skin and attached sub-

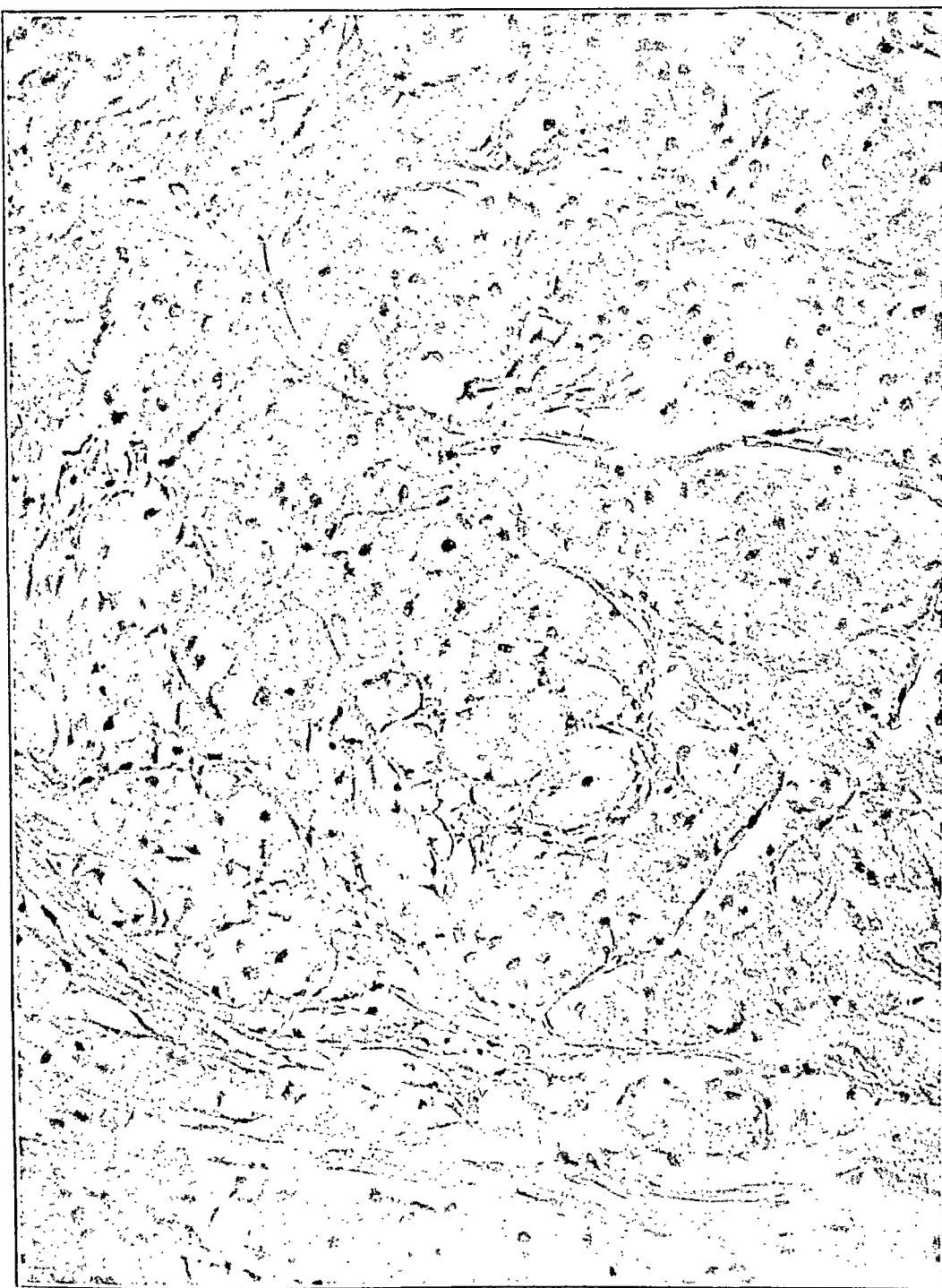


Fig. 4.—Higher magnification of the tumor cells ( $\times 247.5$ ), showing typical myoblastoma cells.

cutaneous tissue. The largest measured 2 by 1.5 cm. On section it contained a small localized firm grayish nodule, measuring 1.5 by 1 cm. Microscopic sections showed a tumor essentially identical with the one removed previously from

the lip except that it was situated deeper in the corium and did not approach the overlying epithelium, from which it was separated by the papillary and subpapillary layers of the corium (fig. 2). The tumor was well localized, but again neither encapsulated nor sharply circumscribed. Groups of tumor cells were seen at the periphery, extending between the collagen fibers of the adjacent corium

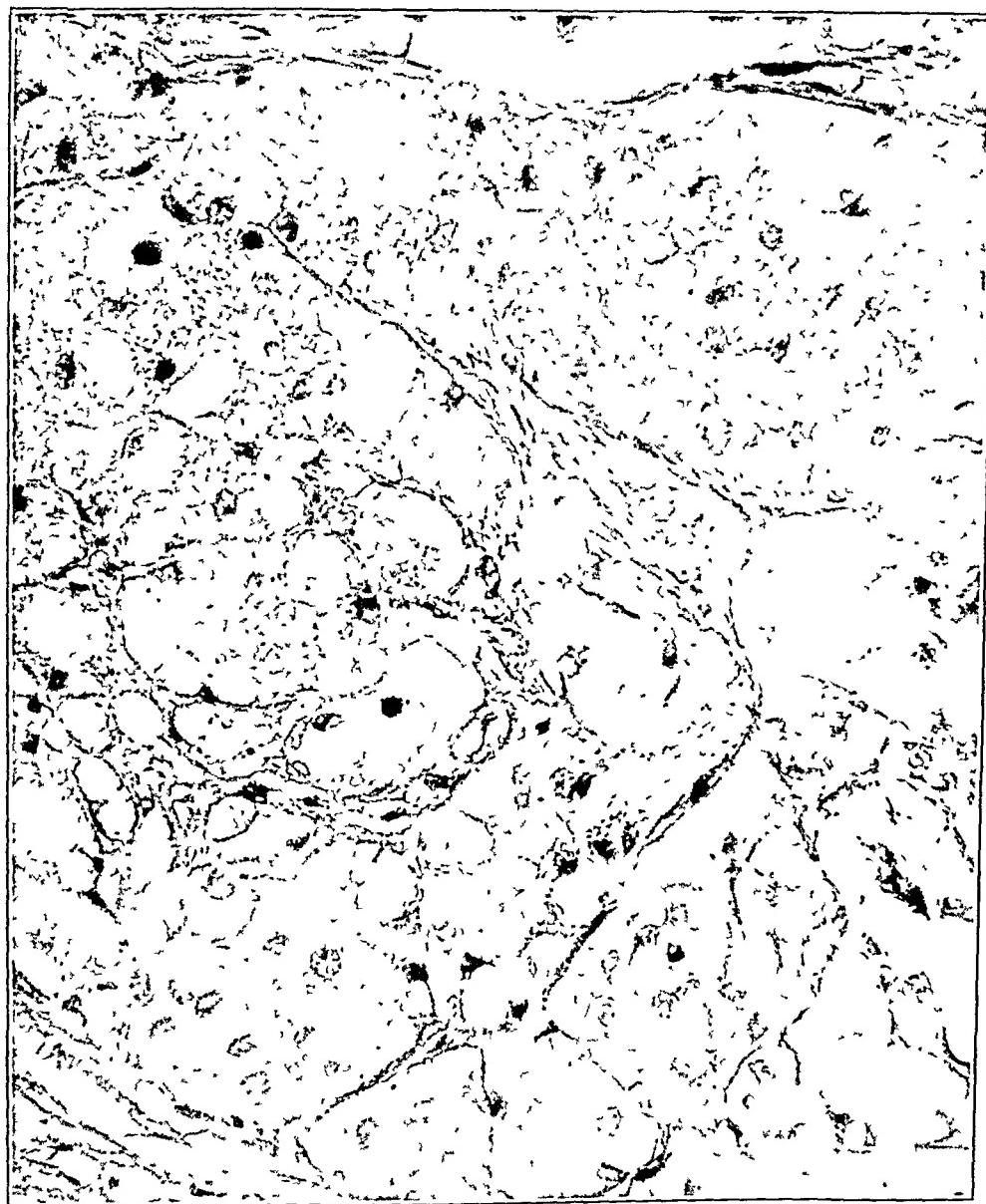


Fig. 5.—Tumor cells in high magnification ( $\times$  approximately 445).

and into the subjacent subcutaneous fat tissue (fig. 3). The tumor cells were large and round, oval or polyhedral. They possessed a considerable proportion of distinctively coarse granular cytoplasm and relatively small and round, oval or somewhat angular nuclei, with a moderate amount of chromatin network and occasionally containing a nucleolus. No mitoses were seen. The cytoplasmic granules varied in density. Where they were more loosely arranged the cells

sometimes had a foamy or vacuolated appearance, but no fat was seen in frozen sections stained with Sudan IV (figs. 4 and 5). The tumor cells were fairly compact except for residual isolated collagen bundles and sweat ducts; in places they were arranged in nests and pseudoalveolar pattern by fine fibrillar trabeculae. The overlying stratified squamous epidermis showed no significant change except for a small focal area of superficial ulceration.

The other two biopsy specimens were slightly smaller, but showed an essentially identical lesion, grossly as well as microscopically.

The microscopic diagnosis was multiple myoblastomas of the skin.

#### COMMENT

The main point of interest in our case is the considerable proliferation of the overlying epithelium of the lip, which led the pathologist to consider the diagnosis of myoblastoma associated with an early prickle cell epithelioma. This feature is not unusual in myoblastoma, for there is frequent mention in the literature of this tendency to excessive hyperplasia of the skin or mucous membrane overlying the myoblastoma. Keynes<sup>18</sup> was first to call attention to this feature, and Klemperer<sup>12</sup> showed the same phenomenon in his cases, some of which resembled early squamous cell epithelioma. Squamous cell epithelioma of the mucosa, overlying a myoblastoma of the tongue, was reported by Schirmer.<sup>19</sup> A similar case was described by Eickhoff<sup>20</sup> and 2 such cases by Leroux and Delarue.<sup>21</sup>

Our case resembled some of those reported by Klemperer which showed the features of squamous cell epithelioma, but because of lack of atypia of the cells and of mitoses, a diagnosis of squamous cell carcinoma was not made. The absence of any changes in the previous tumor area in the lip during a period of two years also strengthens our assumption that the proliferative changes in the epithelium overlying the tumor of the lip are not to be considered as malignant.

Our case presents another point of interest, namely, that of multiplicity of tumors. Myoblastoma is usually a solitary tumor. But in the case of Ebert and Slepian<sup>3</sup> and of Crane and Tremblay<sup>9</sup> there were several lesions at the same site. These authors, however, denied the existence of cases in which multiple myoblastomas occur at more than one place in the same patient. Possibly the case of Powell<sup>4</sup> would contradict this statement. For there were in this case numerous subcutaneous tumors on the face, trunk and extremities, in addition to

18. Keynes, G.: Rhabdomyoma of the Tongue, *Brit. J. Surg.* **13**:570 (Jan.) 1926.

19. Schirmer, R.: Ueber ein Myoblastenmyom zusammen mit Cancroid der Zunge, *Beitr. z. path. Anat. u. z. allg. Path.* **89**:613, 1932.

20. Eickhoff, H.: Myoblastenmyom und Carcinom, *Virchows Arch. f. path. Anat.*, **304**:432, 1939.

21. Leroux, R., and Delarue J.: Sur trois cas de tumeurs à cellules granuleuses de la cavité buccale, *Bull. Assoc. franç. p. l'étude du cancer* **28**:427, 1939.

those in the ovaries and in the retroperitoneal space. Although Powell considered the tumors metastatic, we do not exclude the possibility that these tumors are not metastatic but coincidental and independent of each other. Our case is an example of multiple myoblastomas at different locations.

#### SUMMARY

Myoblastoma is described clinically and histologically. The theories in regard to the nature of this tumor, the question of its possible malignant behavior and the tendency of the overlying epithelium to proliferation and malignant degeneration are discussed.

A case of myoblastoma of the lip is reported, which was followed by multiple cutaneous tumors. Two features of our case are emphasized, namely, the squamous cell epithelioma-like changes in the overlying epithelium of the lip and the multiplicity of lesions.

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## SARCOID OF BOECK IN THE NEGRO

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SARCOID of Boeck is a hematogenous infectious disease, possibly of tuberculous origin and occurs with greater frequency in Negroes than in white persons. This disease is not peculiar to Negroes, but in these patients there is a higher incidence of generalized cutaneous involvement, commoner development of sarcoid tumors on the skin, more frequent formation of well circumscribed and diffuse subcutaneous lesions and more extensive disease of the internal viscera. Despite the universal distribution of lesions these patients are usually asymptomatic and in relatively good health at least during the early phases of the disease.

The roughly symmetric multiform eruption consists of depigmented, hyperpigmented, pinkish or reddish papules and nodules, which have a decided tendency to group and coalesce to form plaques of various sizes and shapes. Pinhead-sized lichenoid lesions are often noted during the phase of resolution. Flesh-colored subcutaneous lesions likewise vary as to size and configuration, and the diffuse subcutaneous infiltrations of the fingers and toes, while not common, are rather distinctive of this disease. The latter, often asymmetrically arranged, are associated with decalcification and partial resorption of the phalanges of the affected digits.

The development of facial lesions is noted frequently, and their preference for the eyelids exclusive of their margins and the canthi, for the alae nasi and for the vermillion border of the lips has diagnostic significance. In the latter two areas and particularly on the alae nasi a solitary nodule or one of a group may enlarge rapidly to form a boggy smooth or crusted tumor, which may be pedunculated. On rare occasions these tumors may be seen elsewhere on the cutaneous surface. I have not observed ulcerations in these growths despite the constant trauma to which they are subjected.

Pulmonary and mediastinal lymph node involvement are commoner and severer in Negroes; in fact, pulmonary lesions are invariably present whenever the cutaneous eruption has assumed generalized proportions. Osseous sarcoid is considered commoner in white patients,<sup>1</sup> yet this

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From the Department of Dermatology and Syphilology of Harlem Hospital,  
Dr. Oswald La Rotonda, Medical Director.

1. Thomas, C. C.: Sarcoidosis, Arch. Dermat. & Syph. 47:58 (Jan.) 1943.

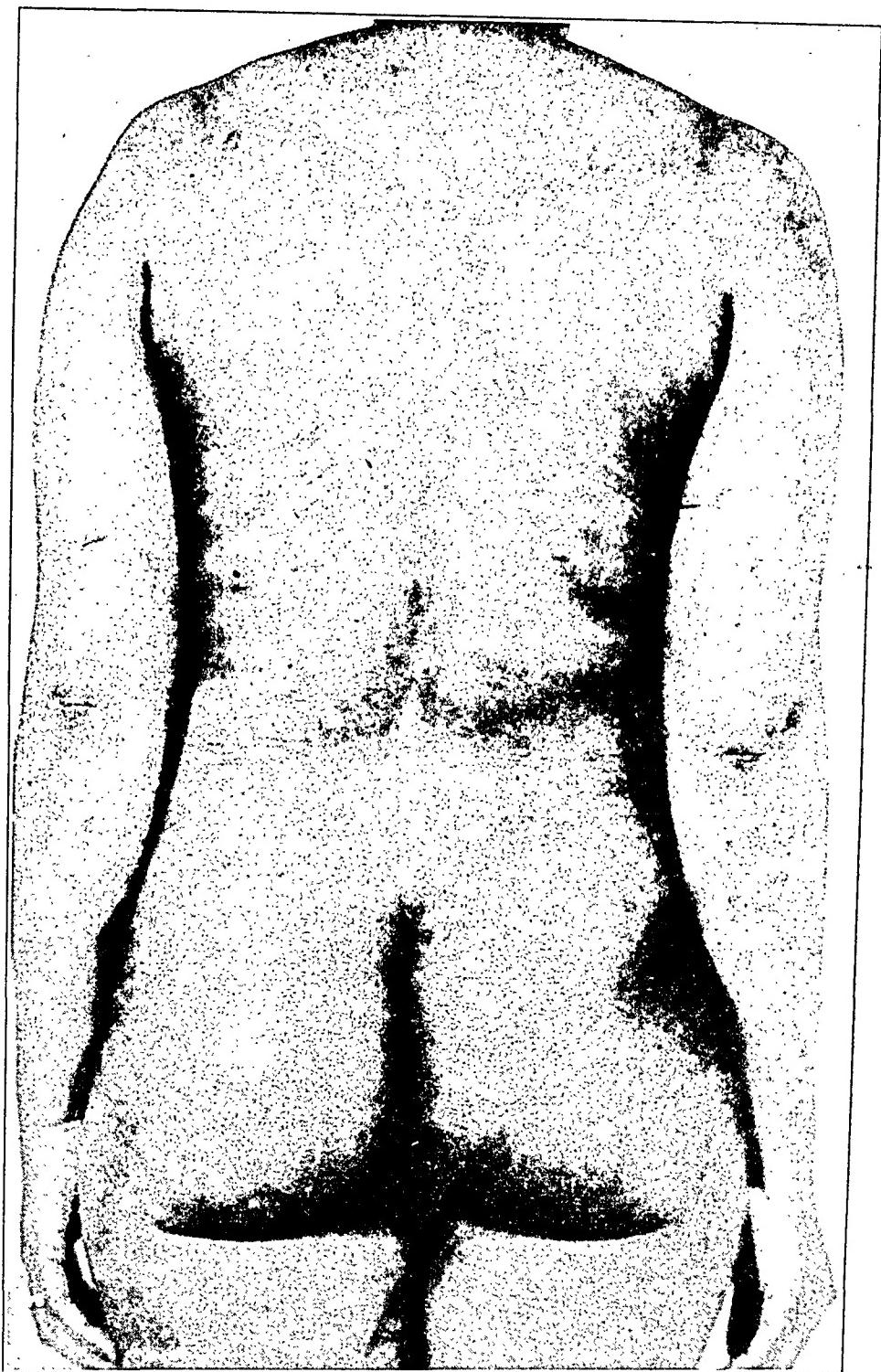


Fig. 1.—Sarcoid of Boeck, showing the generalized character of the eruption.

opinion may have to be revised when one considers the large number of Negro patients with such lesions presented before the various dermatologic societies.

It is generally conceded that Negroes are more sensitive to tuberculin than white patients, and even in sarcoid, in which positive anergy is the rule, Negroes may be hypersensitive to this substance at the outset. In these patients, tuberculin therapy may prove beneficial and a clinical cure may be obtained.<sup>2</sup> The reversal of a positive anergic state to one of hyperergy is often associated with resolution of the cutaneous eruption, and here the prognosis becomes variable. It indicates either a spontaneous clinical cure or the onset of an active tuberculous process in the internal viscera which may ultimately prove fatal.



Fig. 2.—Facial lesions, displaying early tumor formation.

The general histologic features of sarcoid of Boeck do not differ from those seen in sections from white patients, except possibly for the greater tendency in Negroes for the specific infiltrate to coalesce and to develop in greater abundance in the middle and deep layers of the cutis and to invade the subcutis as discrete but more often as conglomerate masses producing clinically the so-called subcutaneous lesions. The sarcoid tumor consists of massive infiltrations of epithelioid cells, the result of coalescence of rapidly forming epithelioid tubercles and, in addition, variable numbers of small lymphocytes, plasma cells and poly-

2. Irgang, S.: Sarcoid of Boeck: Report of a Case of Generalized Cutaneous Distribution and Pulmonary Involvement, with Clinical Cure with Tuberculin, Arch. Dermat. & Syph. 40:35 (July) 1939.

mophonuclear leukocytes. The latter are present in the superficial layer of the cutis and probably indicate local trauma and/or secondary infection. Vascular thromboses may be noted. The intact atrophic epidermis may contain microabscesses and crusts. I have not observed necrotic changes within the cutis, although this pathologic alteration has been reported.<sup>3</sup>

Sarcoid of Boeck must be differentiated from chronic miliary tuberculosis and the sarcoid type of leprosy. The presence of nodules on the

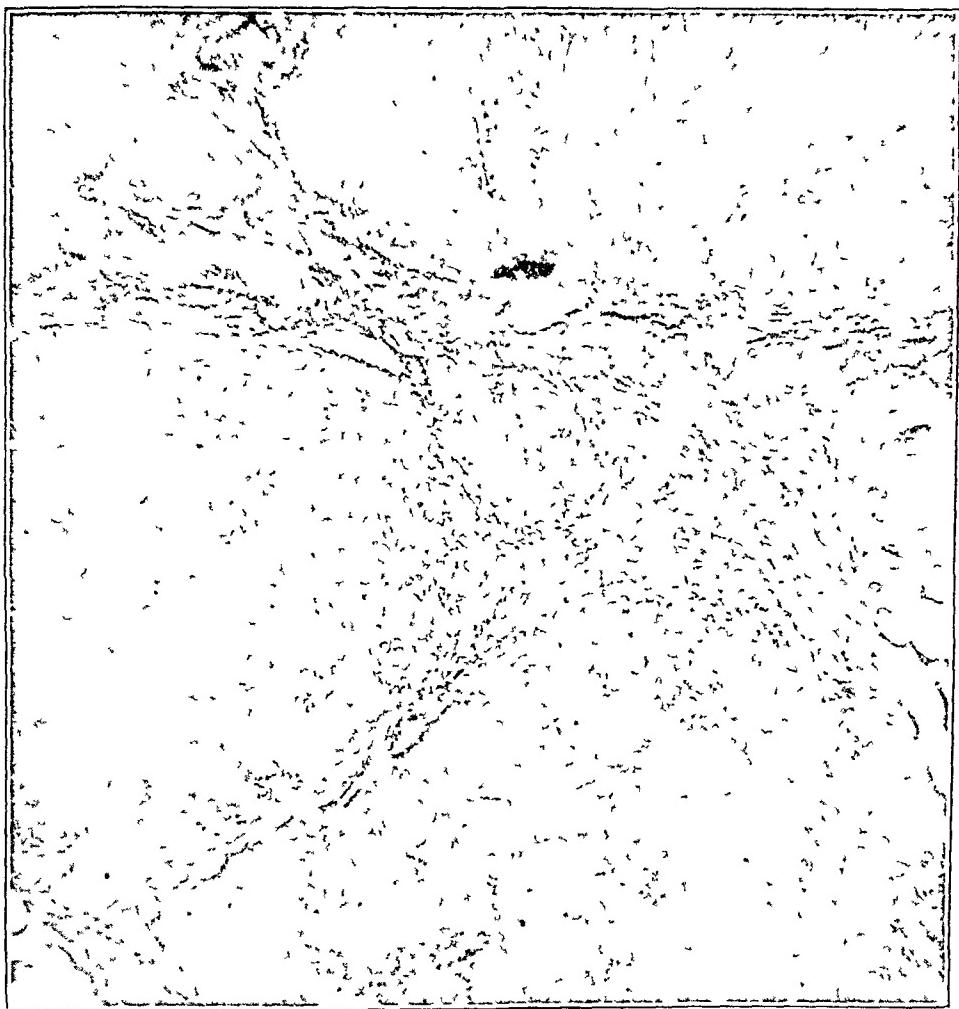


Fig. 3.—Massive epithelioid cell infiltrate, extending from the deep layer of the cutis into the subcutis.

canthi and on the free margins of the eyelids and the absence of subcutaneous lesions and solitary cutaneous tumors favor a diagnosis of chronic miliary tuberculosis. Roentgenographic examination of the lungs is of no diagnostic assistance since the lesions of both have identical

3. Weidman, F. D.: Personal communication to the author; cited by Ronchese, F.: Sarcoidosis and Tuberculosis, Arch. Dermat. & Syph. 46:860 (Dec.) 1942.

appearances. Histologic confirmation of chronic miliary tuberculosis is attained by the observation of small zones of necrosis in the superficial layer of the cutis, oftenest of the caseous variety. In the absence of necrotic phenomena this diagnosis is still tenable when the epithelioid tubercles are almost entirely within the papillae and subpapillae.

Differentiation from the sarcoid type of leprosy rests chiefly on clinical grounds, since the histologic alterations are practically identical



Fig. 4.—Section of a nodule, showing transition to the tumor stage.

and acid-fast bacilli are absent in sections of both diseases. This similarity applies as well to the roentgenographic evidences of pulmonary and osseous involvement.<sup>4</sup> A combination of the following clinical observations favors unquestionably a diagnosis of tuberculoid leprosy:

4. Rabello, F. E.: A lepra incaracteristica no experiencia do Sanatorio Padre Bento, Rev. brasil. de leprol. 11:115 (June) 1943.

enlargement of the ulnar and great auricular nerves, hyperesthesia in recent cutaneous lesions, anesthesia of cutaneous lesions to extremes of temperature and often to touch, atrophy of the interosseous muscles, wrinkling of the skin on the back of the hands and thinning of the eye-brows.

#### COMMENT AND SUMMARY

Sarcoid of Boeck is observed more frequently in Negroes, but this should be expected in view of the likely tuberculous causation for this

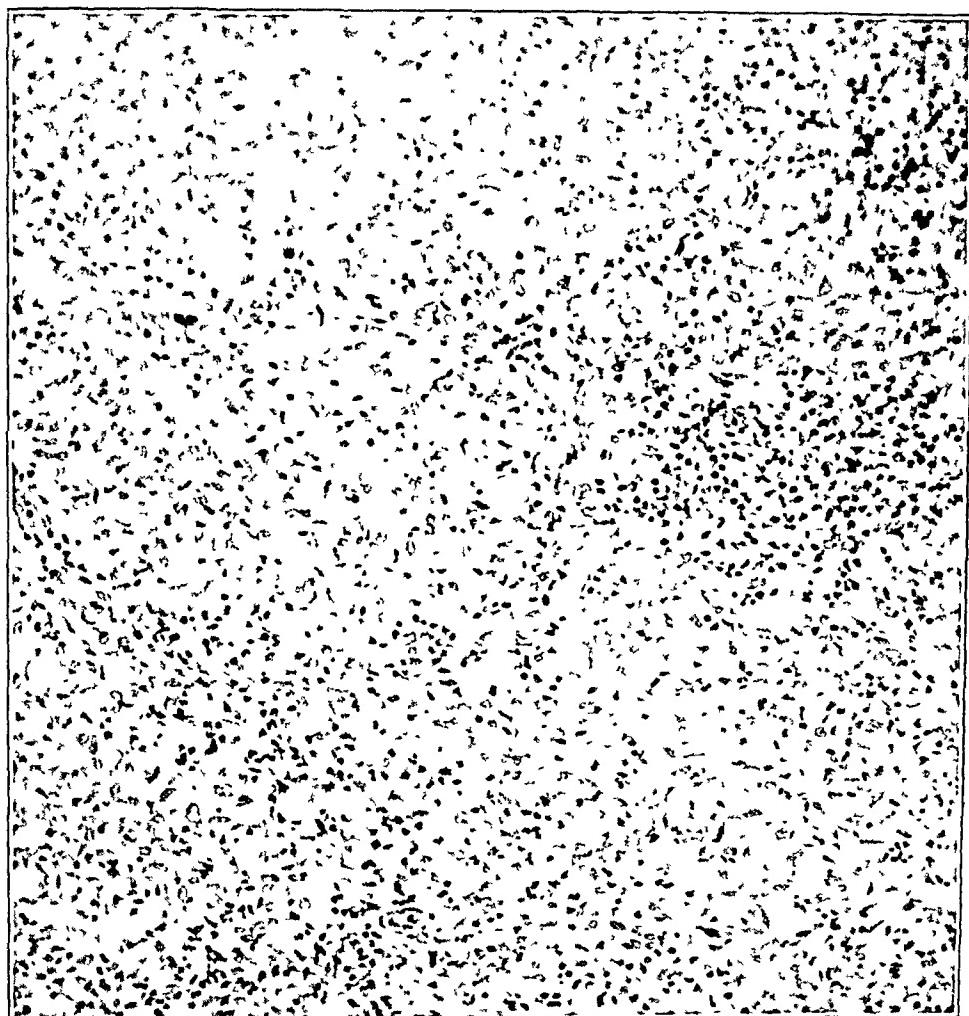


Fig. 5.—High power view of a fully developed sarcoid tumor, showing the diffuse character of the epithelioid cell infiltrate.

disease. It is acknowledged that the incidence of tuberculous infection is greater in them than in white persons, but in spite of the higher degree of tuberculin sensitivity the resistance is much lower in Negroes. This unfavorable immunobiologic response is responsible for the more widespread and severer type of infection and for the less favorable outlook.

Regardless of race, sarcoid of Boeck is a relatively benign, slowly progressive and recalcitrant disease which often terminates in a clinical cure. Its transformation to frank tuberculosis occurs in a minority of instances, and those cases which have been reported as terminating fatally have occurred oftener in Negroes.

Sarcoid of Boeck is not peculiar to Negroes. Similar lesions occur in both races, but generalized cutaneous eruptions and solitary cutaneous tumors are noted more often in Negroes. This applies also to the incidence of well defined subcutaneous lesions and to the diffuse subcutaneous infiltrations of the digits, associated with partial resorption of the affected phalanges.

The histologic alterations are also similar, but in Negroes there is a decided tendency for the epithelioid tubercles to coalesce and for the specific infiltrate to develop with greater intensity in the deep layer of the cutis and to involve the subcutis secondarily.

Sarcoid of Boeck must be differentiated from chronic miliary tuberculosis and the sarcoid type of leprosy. Predilection of lesions for the face is common to both sarcoid of Boeck and chronic miliary tuberculosis, but their development on certain regions of the eyelids is distinctive for each disease: the eyelids proper for the former and the free margins and canthi for the latter. Differentiation from the sarcoid type of leprosy depends almost entirely on clinical observations, since the histologic and roentgenographic observations are inconclusive.

160 Riverside Drive.

## COSMETIC DERMATOLOGY

### Alkalinity of Face Powder Mixtures

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OR IS it dermatologic cosmetology? Since cosmetics have achieved the dignity of a "logos," as confirmed by courses in cosmetology at universities, more helpful cooperation between the practitioners of the cosmetic art and dermatologists is desirable. Unfortunately, the art and practice of cosmetics cannot be divorced from the fanciful and glamorous sales promotion required by the cosmetic industry. Fearful of being caught in these promotional exuberances dermatologists have tended to shy away completely from even their legitimate interest in the scientific phases of cosmetics. This has been unfortunate since now complete aloofness is impossible.

The Federal Food, Drug and Cosmetic Act of 1938 specifically defines drugs and cosmetics; the former as allegedly or demonstrably able to influence structure or function and the latter as possessed only of properties to influence appearance or the state of cleanliness. Since labels on cosmetics were happily disregarding such distinctions, the industry found itself in conflict with the law.

Finding themselves, in terms of the new law, possessed of items classified as drugs in their merchandise, the cosmetic manufacturers persisted not only in selling these items by adequate revision of labels but in seeking further for drug products applicable for sale by the industry. If, they argued, a product contains a drug the action of which, in topical application, will improve the appearance of the skin and if such practice is safe without immediate medical supervision, such a product is a cosmetic and they proposed to sell it. There may be room for argument as to whether this is good public policy, but it is legal and is being done. Manufacturers must have medical guidance for all these "drug cosmetics" and, at times, medical evidence both as to the safety and efficiency under the "directions for use." The leaders and pioneers in the industry have, with liberal hand, sought such advice and have undertaken such studies.

Nor is this the only manner in which dermatologists serve the industry. Many dermatologic reports have pertinent cosmetic implication or application either from the facet of advertising or the compo-

sition of the product. Studies of ionization of the surface of the skin have been of interest in the cosmetic industry. The study reported below was inspired by that interest.

Disclosure of the acid character of the cutaneous surface and the secretions thereon has led to the opinion that the regular application of alkaline substances to this surface may be the background for simple dermatitis or for the maintenance of it. For this reason more than any other, soap has been stigmatized as deleterious to eczematous

*Potentiometric Measurements of Various Suspensions of Face Powder and Talcum in Distilled Water*

Sample No.	Color of Sample*	5 Gm. Powder plus 25 Cc. Water		10 Gm. Powder plus 25 Cc. Water	
		Mixture <i>pH</i>	Liquid <i>pH</i>	Mixture <i>pH</i>	Liquid <i>pH</i>
1.....	3	8.40	8.43	....	....
2.....	1	9.25	....	9.20	9.20
3.....	3	9.10	9.13	....	....
4.....	4	8.76	8.80	....	....
5.....	1	8.72	8.35	....	....
6.....	1	9.00	8.00	....	....
7.....	3	7.90	7.92	....	....
8.....	2	9.00	9.20	....	....
9.....	1	8.94	....	8.90	....
10.....	4	9.42	....	9.42	....
11.....	2	9.06	....	....	....
12.....	2	9.18	....	....	....
13.....	3	9.30	....	8.84	....
14.....	3	8.78	....	....	....
15.....	3	7.70	....	....	....
16 (Costly face powder deliberately striving for neutral mixture).....	2	7.19	....	....	....
17 (French talcum).....	..	9.02	....	....	....
18 (Domestic talcum).....	..	9.43	....	....	....
19 (Jaipur India talcum).....	..	8.38	....	....	....

\*Colors were matched and identified by numbers. To reveal the product shade name would in some cases identify the product.

or "sensitive" skin. I have elsewhere<sup>1</sup> expressed myself as unconvinced of any danger from the alkalinity of toilet soap.

As added evidence that the skin tolerates habitual exposure to moderate degrees of alkalinity, ionization measurements on suspensions of face powders, the most generally used of all cosmetic preparations, are given in the accompanying table. These tested preparations were bought in the open market. They are on sale at popular prices in chain stores and for that reason have wide patronage.

The alkaline reaction is due to (1) the slight alkaline contamination of the talcum, (2) the character of the added pigment and (3) possibly

1. Sharlit, H.: Soap and the "Soap Problem," New York State J. Med. 43: 160 (Jan. 15) 1943.

the chemical nature of the perfume. While it is true that neutral mixtures could be achieved if striven for, acceptance by consumers of the products as they are does not justify such effort. Here, then, is a cosmetic practice, as general as the use of toilet soap, that supplies the cutaneous surface continuously with a source of alkalinity. Add this fact to the established clinical experience that the use of face powders is by and large the safest of all cosmetic practices, and one should unhesitatingly believe that slight alkalinity in mixtures habitually applied to healthy skin is absolutely safe.

The table of measurement requires no comment other than a description of the procedure followed in the preparation for measurement. Twenty-five cubic centimeters of distilled water was added to 5 Gm. of powder, the mixture shaken in a corked 50 cc. flask, allowed to stand over night at room temperature, then shaken vigorously and the  $p_H$  of the water-powder mixture determined with a Coleman potentiometer. The  $p_H$  of some samples was, in addition, determined on suspensions in which 10 Gm. of powder was suspended in 25 cc. of distilled water. With eight of the samples an added procedure involved centrifugation of the mixture, with use of the clear liquid secured by careful pipetting, for determinations of the  $p_H$ .

32 East Sixty-Fourth Street.

## PSEUDOEPITHELIOMATOUS HYPERPLASIA DUE TO GRANULOMA INGUINALE

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IT IS surprising that the literature in this country contains so many references to a disease as comparatively rare as granuloma inguinale. The fact that there are still outstanding gaps in our knowledge of this disease probably is intriguing and inspires continued investigation. Recently Gordon<sup>1</sup> reported on a study of 200 cases and concluded, in essence, that not all the factors of its epidemiology are known, that no known drug completely eradicates the Donovan bodies and that further research is necessary before a cure is discovered.

The clinical diagnosis is seldom difficult. The usual picture is that of a chronic infective granuloma, located in nearly all cases on the genitalia and exhibiting destructive ulcerative properties, the progress of which is generally slow but continuous. Hyperplasia is not usual. Reference is made, however, to hypertrophic and cicatricial lesions by D'Aunoy and von Haam.<sup>2</sup>

Contrary to the ease of clinical diagnosis, its confirmation by laboratory methods is often difficult, especially when the tissue to be examined is of superficial origin. Of 150 cases reviewed by Fox,<sup>3</sup> 15 of which were his own, "The diagnosis was confirmed in eleven cases by the presence of the Donovan bodies in smears. The latter were generally obtained from the deeper parts of tissue removed for histologic examination."

This paper has a twofold purpose: first, to report a case of granuloma inguinale with decided hyperplasia rather than destruction of the tissues and, second, to emphasize the necessity for repeated search for Donovan bodies, even over a period of months, in all suspected cases.

1. Gordon, G. A.: Granuloma Inguinale: A Study of Two Hundred Cases, J. M. A. Georgia **35**:105-107 (April) 1946.

2. D'Aunoy, R., and von Haam, E.: Granuloma Inguinale, Am. J. Trop. Med. **17**:747-763 (Sept.) 1937.

3. Fox, H.: Granuloma Inguinale: Its Occurrence in the United States, J. A. M. A. **87**:1785-1790 (Nov. 27) 1926.

## REPORT OF A CASE

E. G., a white man, aged 39, entered Colorado General Hospital for the first time on June 21, 1944, complaining of cauliflower-like growths on the penis.

The following history was taken. Several years prior to admission he noticed a wartlike mass on the mucosal surface of the foreskin. Soon thereafter two similar lesions appeared near the initial lesion. These lesions were each about the size of a pea and produced no discomfort. The lesions slowly grew to about the size of a marble, became ulcerated and projected to the cutaneous surface on the shaft. Pain and tenderness were moderate. There was generalized swelling of the organ. The patient gave no history of venereal disease and denied extramarital sex exposure. He was employed as a truck driver and had, in the course of his duties, driven all over the southwestern states and Mexico.



Fig. 1.—Penis during first period of hospitalization. The firm cauliflower-like lesions were of over four years' duration.

Physical examination revealed no abnormalities except the penile growths. There was no involvement of the inguinal glands, scrotum or scrotal contents. The dorsum of the shaft of the penis presented three ulcerative cauliflower-like masses, each about the size of a fifty-cent piece. The lesions (fig. 1) were grayish-white and pinkish. Each mass was moderately firm, discrete and friable and oozed on slight trauma. From the periphery of these lesions pus could be expressed with light pressure.

Diagnoses considered on admission were (1) deep mycotic infection and (2) carcinoma.

*Laboratory Investigation*.—Smears and cultures of the foul-smelling purulent exudate revealed the presence of *Staphylococcus aureus*. Dark field examination showed many nonpathogenic saprophytic spirochetes. Reactions in the following tests were negative: Mantoux test (old tuberculin in dilutions of 1 to 1,000 and

1 to 10,000), Frei test, complement fixation test for gonorrhea, Kolmer and Eagle serologic tests and *Bacterium tularensis* agglutination tests (serum in dilutions of 1 to 50 and 1 to 200). The leukocyte count was 14,200, with a normal differential count. The sedimentation rate was 57 mm. in one hour. Results of other laboratory tests were not remarkable.

*Pathologic Report.*—Gross Description: The specimen consisted of a small wedge of skin and underlying tissue, the total measuring 1 by  $\frac{1}{2}$  by  $\frac{1}{2}$  cm.

Microscopic Examination: Sections showed a greatly thickened stratified squamous epithelial layer, with moderately dense fibrous connective tissue beneath. The epithelial layer was folded back on itself and was greatly thickened. The normal rete cones were replaced by broad bands of cells extending into the con-

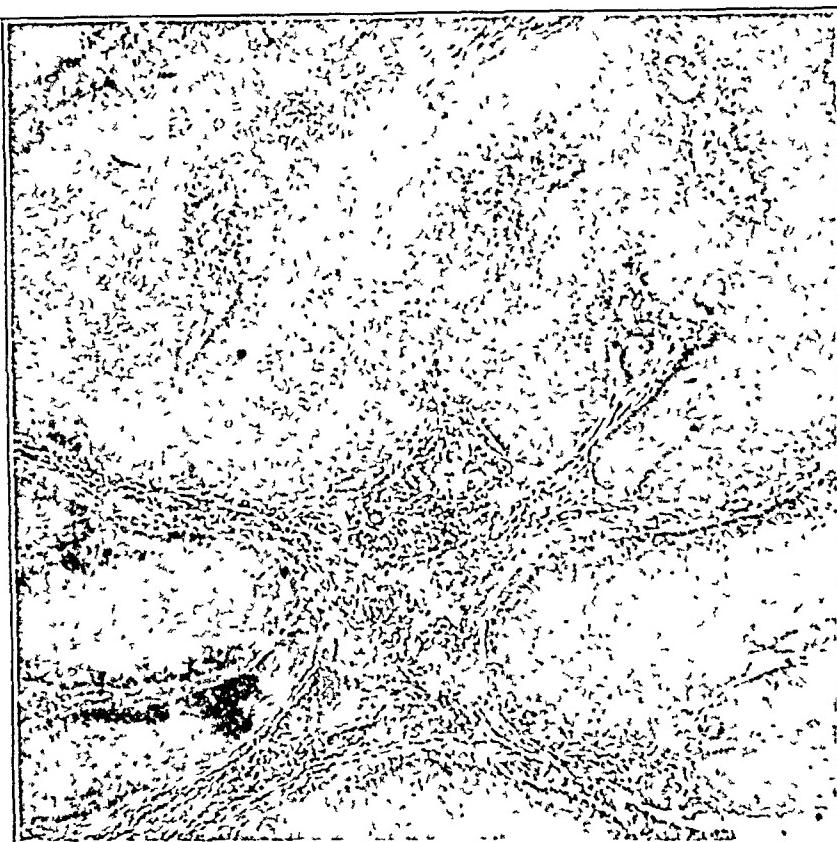


Fig. 2.—Photomicrograph ( $\times 120$ ) showing dense fibrous connective tissue beneath a greatly thickened stratified epithelial layer. Pathologic diagnosis: squamous cell papilloma.

nective tissue. The basal layer of epithelial cells was well demarcated from the underlying connective tissue. The papillae were elongated, somewhat dilated and vascular. A few segmented neutrophils were present in the epithelial layer. In the underlying connective tissue were moderate numbers of lymphocytes, plasma cells and segmented neutrophils diffusely infiltrating the tissue.

In the hyperplastic epithelium in a section stained by Levaditi's method were scattered spirochetes which did not conform in their structure to *Treponema pallidum*. The organisms were shorter, fairly widely undulated in their folds and blunted at their ends. The pathologic diagnosis was squamous cell papilloma of the penis.

*Bacteriologic Investigation.*—Lymph nodes were removed and carefully studied, sections of this material were ground up and examined by direct smear, and

various laboratory animals were inoculated with the material. No significant observations resulted from these extensive efforts.

*Treatment*.—The patient received penicillin locally in the form of wet packs and was given penicillin systemically in a dosage of 20,000 units every four hours for nine consecutive days. No demonstrable change was effected. This was followed by an intensive course of oxophenarsine hydrochloride therapy. No change was noted. On the theory that the disease might be a deep mycotic infection, the patient then received roentgen ray and iodide therapy. A total of 6,000 r was given to the involved area in fractional doses of 1,000 r each at a peak of 100 kilovolts with 1 mm. of aluminum. Iodide therapy consisted of saturated solution of potassium iodide, beginning with 4 drops three times a day and gradually increased



Fig. 3.—Penis thirteen months after the first examination, showing hyperplastic mass.

until the patient was receiving 20 drops three times a day, on which he was maintained for ten days. No change in the patient's disease or appearance was apparent.

Pathologic slides (fig. 2) were sent to the Department of Cutaneous Medicine, Laboratory of Dermatological Research, University of Pennsylvania, with the request that aid be given in establishing a diagnosis. The pathologists stated that they too were unable to make a diagnosis from the study of the slides, but were of the opinion that the disease was of virus origin and might be in the nature of a malignant papilloma or condyloma acuminatum. Because of this indication, a tissue suspension prepared from fresh biopsy material was injected into laboratory animals intracranially and intraperitoneally. Results of autopsies of these animals were negative. A tissue vaccine of similar material was prepared, and 0.1 cc. was given intradermally, without untoward reaction. The patient was discharged

*Pathologic Report.*—Gross Description: The specimen consisted of six irregularly-shaped pieces of tissue, which were brown with 1 to 2 mm. islands of firm hard yellow-gray tissue. The largest piece of tissue measured 8 mm. in diameter. The cut section was lobular, firm and gray.

*Microscopic Examination*—The sections showed skin in which the rete pegs were wide and extended deep into the dermis. There was a sharp demarcation between the germinal layer and the dermal connective tissue. The stratum lucidum was absent in many areas. Acanthosis was present in the germinal layer, mitotic figures being seen in the deeper layers. The fibrous connective tissue of the papillae was dense with hyalinization of the collagen fibers and infiltration with lymphocytes and polymorphonuclear cells. No Donovan bodies were seen with hematoxylin



Fig. 5.—Penis after one month's treatment with antimony and potassium tartrate. Most of the raw surface is covered with a healthy-appearing epithelium.

and eosin or Giemsa stains. The pathologic diagnosis was papilloma of the skin of the penis, squamous type.

Freshly obtained tissues were especially studied to determine whether Donovan bodies were present. None were seen either in tissue sections or tissue smears.

*Course.*—The patient was seen in the Tumor Conference for a full review of the history and observations. Radical surgical treatment was advised. The genito-urinary department made a diagnosis of carcinoma-like condyloma acuminata of Buschke-Lowenstein type, with the recommendation of surgical removal of the granulomatous mass. He was transferred to that department temporarily, and under general anesthesia a two stage electrosurgical resection of the penile redundant tissue was done.

The resected tissue was sent to various laboratories for further studies, especially to determine whether Donovan bodies were present. From these tissues, the

pathologic diagnosis remained the same: squamous cell papilloma. However, tissue smears of the most deeply resected tissue revealed numerous Donovan bodies (fig. 4). Bacteriologic examinations of the tissue by culture and inoculation of animals revealed nothing significant.

*Further Treatment.*—After the observation of Donovan bodies, the patient was given an aqueous solution of 1 per cent antimony potassium tartrate injected intravenously every other day, beginning with 1 cc. and increasing the dose by 1 cc. with each injection until the maintenance dose of 10 cc. was reached. The raw oozing surface soon began to epithelize. Locally antimony potassium tartrate was not tolerated, even in dilutions as high as 1 to 10,000, so wet packs of "chloresium solution-plain" were used.

It was soon apparent that a small opening had been made in the floor of the urethra, just posterior to the glans penis, by the electrosurgical procedure. Treatment directed to remedy this was refused by the patient. Small areas of exuberant epithelium were easily controlled by painting with a solution of 20 per cent resin of podophyllum in 95 per cent alcohol. He was maintained on antimony potassium tartrate therapy for one month. The lesions were epithelizing (fig. 5), and this satisfactory therapeutic result was taken as further confirmation of the correctness of the diagnosis. The patient was discharged on September 6, with instructions to return weekly for intravenous injections of 1 per cent aqueous solution of antimony potassium tartrate.

One week later he reported as directed, but complained that the day after he was discharged his wrist had become "paralyzed." Neurologic examination revealed a radial nerve wrist drop (right) due to conversion hysteria.

The patient did not return again, nor did he seek any other medical aid. Four months later there was a regrowth of granulomatous tissue all about the penis, but again he refused hospitalization.

#### COMMENT

The disease in this case was undiagnosed for months, because the clinical appearance was that of a hyperplastic epitheliomatous process rather than a destructive ulceration and because assiduous attempts to find Donovan bodies were futile until the entire granuloma was removed, when Donovan bodies were demonstrated in abundance in the deeper recesses of the removed tissue.

#### SUMMARY

A case of granuloma inguinale of the penis in a white man aged 39 is presented. Clinically, the disease in its early stages resembled blastomycosis and later carcinoma. The disease was undiagnosed for months in spite of extensive laboratory investigation and repeated efforts to demonstrate Donovan bodies. The eventual diagnosis was made after observing Donovan bodies deep in tissue removed en masse by electrosurgical resection. Treatment consisted of electrosurgical resection of the granuloma, antimony potassium tartrate given intravenously and resin of podophyllum administered locally. Cessation of treatment for a period of four months resulted in a recurrence of the original ulcerative granuloma.

## DERMATITIS VENENATA DUE TO STREPTOMYCIN

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AND

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IN JANUARY 1944, streptomycin, a new antibiotic agent, was described by Waksman, Bugie and Schatz.<sup>1</sup> Different toxic reactions to the drug have since been reported<sup>2</sup> such as neurotoxic action on the eighth nerve and histamine-like reactions. The minor toxic effects include cutaneous rashes, malaise and fever. The cutaneous reactions have been erythema nodosum and toxic erythema, morbilliform in type.<sup>3</sup> To our knowledge contact dermatitis has not previously been reported.

### REPORT OF A CASE

A white woman aged 32, who was a nurse working at the Veterans Hospital, Kingsbridge Road, Bronx, New York, on a ward in which a research study of streptomycin is in progress, reported to the outpatient clinic on Feb. 17, 1947, complaining of itching, swelling and redness of the eyelids and sides of the neck.

The disease was diagnosed as contact dermatitis, and the patient was given "pyribenzamine hydrochloride" N.N.R. (tripelennamine hydrochloride), 50 mg. three times a day, and a soothing lotion. The disease remained unchanged for two days, until she stopped working. The lesions then subsided rapidly, leaving only residual scaling and erythema. She returned to work on February 24 and again erythema and pruritus of the eyelids, cheeks, sides of the neck and upper part of the chest promptly developed. Similar patches appeared on the hands, fingers and forearms. The patient was referred for consultation on February 28.

When first seen by us the patient presented severe edema of the eyelids. There were ill defined patches of erythema and scaling on the cheeks, chin, neck and upper

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1. Waksman, S. A.; Bugie, E., and Schatz, A.: Isolation of Antibiotic Substances from Soil Micro-Organism with Special Reference to Streptothricin and Streptomycin, Proc. Staff Meet., Mayo Clin. **19**:551 (Nov. 15) 1944.

2. Hetting, R. A., and Adcock, J. D.: Streptomycin: Toxicity for Man; Preliminary Report, Science **103**:355 (March 22) 1946.

3. Streptomycin, report of the Council on Pharmacy and Chemistry, J.A.M.A. **133**:320 (Feb. 1) 1947.

anterior part of the chest. There were similar erythematous scaly patches with minute vesiculation on the flexor aspect of the right forearm, the left wrist and the dorsal surface of all proximal phalanges.

The patient said that she had not been using new cosmetics or other possible external irritants. There was no history of previous allergies. She stated that she had been working with streptomycin since the beginning of 1947, her job consisting of preparing the solutions and giving the injections. Occasionally during the performance of this task her hands came in contact with the solution.

A complete physical examination showed no abnormalities. The urine was normal. The blood count showed 4,000,000 erythrocytes and 8,000 leukocytes. The differential count showed no eosinophils.

Patch tests were performed on February 28 with a solution of streptomycin diluted 1 to 10 in distilled water. The patient was also tested for sensitivity to her cosmetics, including cold cream, "eau d'ecouge," lipstick, rouge, face powder, perfume, nail polish and shampoo. A test was also made with a solution of penicillin. The reactions to all these with the exception of streptomycin, were negative. One hour after application the streptomycin produced local pruritus, and forty-eight hours later it elicited an erythematovesicular reaction. There was also a decided flare-up of the lesions on the face and hands.

The patient stopped handling streptomycin, and the lesions and pruritus began to subside. On March 8 she was allowed to work one day, but was instructed to wear rubber gloves while preparing and giving the injections. There was no exacerbation of the disease.

On March 9 another patch test with streptomycin diluted 1 to 100 in distilled water was made. In forty-eight hours there were erythema and vesiculation, but less than when the 1 to 10 dilution was used. An intradermal test, with streptomycin diluted 1 to 100, resulted in erythema, infiltration and vesiculation in twenty-four hours. There was no exacerbation of the dermatitis.

Ten patients, 5 of them with an allergic background, were given patch tests with a 10 per cent solution of streptomycin. Reactions in all tests were negative in forty-eight and in seventy-two hours.

#### SUMMARY

A case of dermatitis venenata involving the hands, forearms and face in a nurse handling solutions of streptomycin is reported.

**ADDENDUM.**—Since this paper was accepted for publication a total of 3 out of 4 nurses continuously handling streptomycin have experienced dermatitis venenata. The 2 new patients had handled the drug for a period of five months. Many nurses came in contact with the drug for short periods, without dermatitis developing. Further studies on the cutaneous sensitivity to streptomycin and possible desensitization are in progress.

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## CONTACT ECZEMATOUS DERMATITIS AND PATCH TESTS A Histologic Study

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**I**N A previous paper<sup>1</sup> the histology of the eczematoid dermatoses was discussed. Mention was made of the histologic reactions in contact eczematous dermatitis. In this paper a further detailed study will be made. The observations in patch tests will also be considered.

From the histologic standpoint, the term acute dermatitis is used to express an inflammatory reaction confined to the upper third of the cutis and characterized by congestion, edema and cellular infiltration. This infiltration is composed of round cells and wandering connective tissue cells.

The term eczema microscopically refers to a dermoepidermic process, in which there is intraepidermic vesicular formation at some time. In addition to the changes in the cutis there are changes in the epidermis. These changes are (1) intercellular edema, (2) spongiosis and (3) vesicular formation. The horny zone shows patchy areas of parakeratosis.

The term contact dermatitis is a misnomer, since there are histologic changes in the cutis and epidermis. Hence, the term contact eczema would be more proper. However, in this paper the term contact eczematous dermatitis is used to denote pathologically what Sulzberger called eczematous contact type dermatitis.<sup>2</sup>

Clinically the epidermis may be divided into three possible zones where the histologic responses to contact allergens or irritants can be expected: (1) rete malpighii, (2) follicular appendages and (3) sweat ducts. The rete malpighii is the usual seat of the histologic responses. In this paper this type of response will be studied mainly.

The halogens and the heavy metals are among the primary irritants and may produce necrotic reactions about the upper part of the pilo-

1. Sachs, W.; Miller, C. S., and Gray, M.: Histopathology of the Eczematoid Dermatoses, Ann. Allergy 2:289 (July-Aug.) 1944.

2. (a) Sulzberger, M. B., and Wolf, J.: Dermatologic Therapy in General Practice, Chicago, The Year Book Publishers, Inc., 1940, p. 115. (b) Sulzberger, M. B.: Dermatologic Allergy, Springfield, Ill., Charles C Thomas, Publisher, 1940, p. 93.

sebaceous apparatus. It is my impression that the sweat duct system shows a dyshidrotic type of vesicle within the epidermis as a result of a contact irritant response. Further study will be necessary on this subject.

The inflammatory response in contact eczematous dermatitis depends on four factors: (1) the nature of the allergen or irritant involved, (2) the sensitivity of the person involved, (3) the duration of exposure

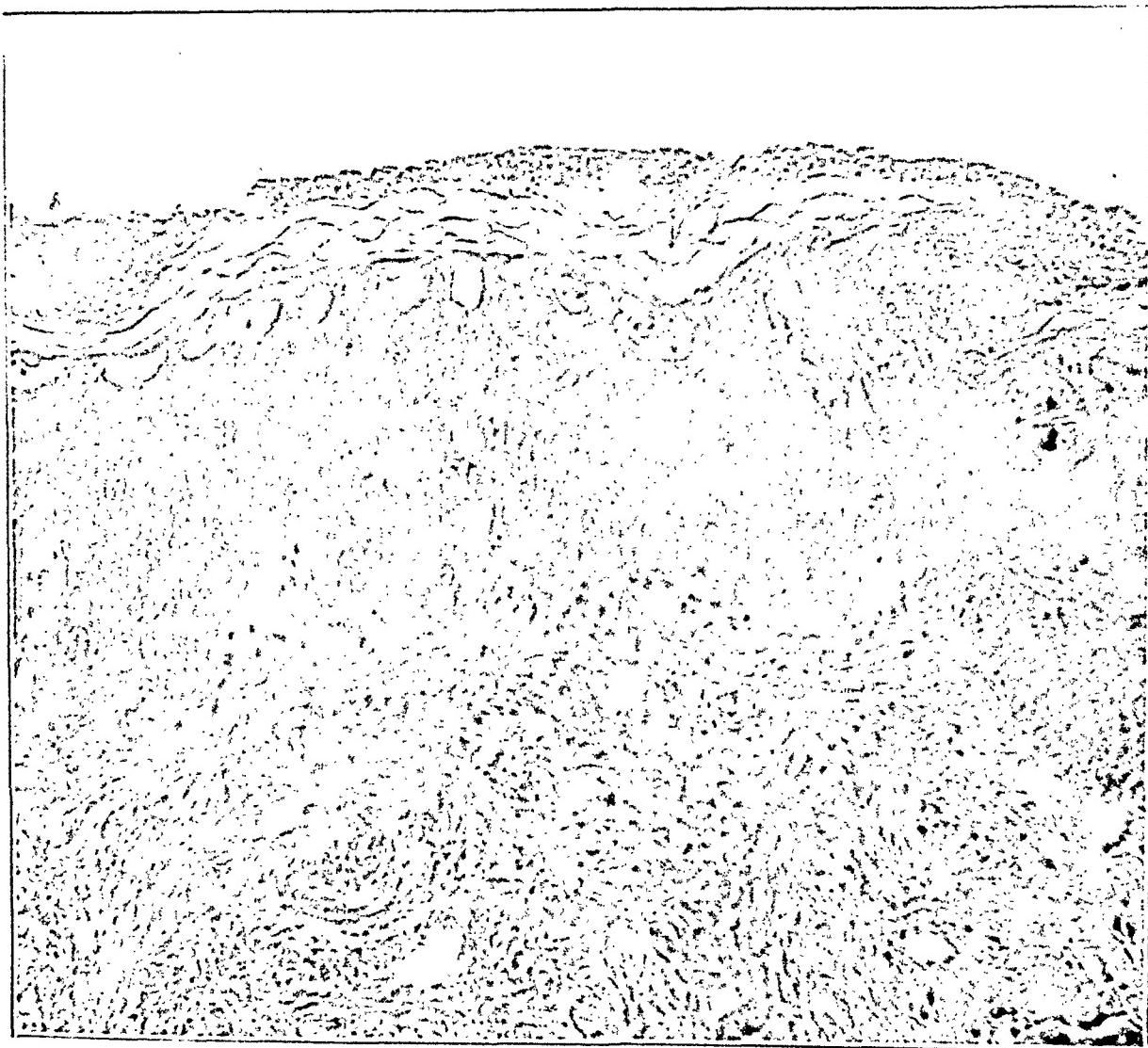


Fig. 1.—Small area of section of dermatitis venenata rhus, showing edematous degeneration of epidermal cells high up in prickle cell zone. ( $\times 100$ .)

or exposures to the irritating substances and (4) the velocity with which the histologic response occurs. This fourth factor depends on the preceding three factors. By velocity of histologic response is meant the rate at which the inflammatory reaction takes place. If slow, the process is milder; if rapid, the reaction is more apt to be intense.

The outstanding feature in eczematoid dermatoses is intraepidermic vesicular formation. In eczema,<sup>3</sup> intercellular edema, spongiosis and vesicular formation are noted. Intercellular edema denotes an exaggeration of the normal flow of lymph; the spaces between the prickle cells are widened, and the prickles stand out. In spongiosis the flow of lymph is more decidedly increased, the pressure is greater, and some of the prickles are broken to form irregular spaces between the



Fig. 2.—Contact eczematous dermatitis, vesicular response. ( $\times 60$ )

cells with a spongelike appearance—hence the name spongiosis. Fusion of these irregular spaces gives rise to true vesicles. This type of formation of vesicles is known as primary vesicular formation. These vesicles contain fluid, a varying number of leukocytes, a few edematous prickle cells and occasionally free epithelial nuclei. They usually occur high up in the epidermis, beneath the horny layer, and they vary in size.

3. Macleod, J. M. H., and Muende, I.: Practical Handbook of Pathology of the Skin, New York, Paul B. Hoeber, Inc., 1940, p. 83.

This group, known as eczema, is not a disease *sui generis*, but probably an expression of several diseases having the same histologic changes.

In acute contact eczematous dermatitis, it appears that the formation of vesicles is due to edematous degeneration<sup>4</sup> of the epidermal cells themselves (fig. 1). The contact allergen or irritant must penetrate into the epidermis, producing parenchymatous edema of the involved



Fig. 3.—Reaction in a patch test with a peroxide mixture. The necrotic response is of the primary irritant type. ( $\times 100$ ).

cells. It is also carried down to the cutis by the lymph producing the congestion, edema and cellular reaction seen there. It is difficult to ascertain whether the changes in the epidermis or cutis initiate the process or whether they occur simultaneously.

4. Macleod and Muende,<sup>3</sup> p. 88.

Two types of histologic responses may be seen in the epidermis in acute contact eczematous dermatitis: (1) vesicular response and (2) necrotic response.

In vesicular response (fig. 2) the following changes are seen microscopically. In the cutis the superficial blood vessels are dilated. There is a perivascular inflammatory reaction composed of round cells and wandering connective tissue cells. An occasional leukocyte may be

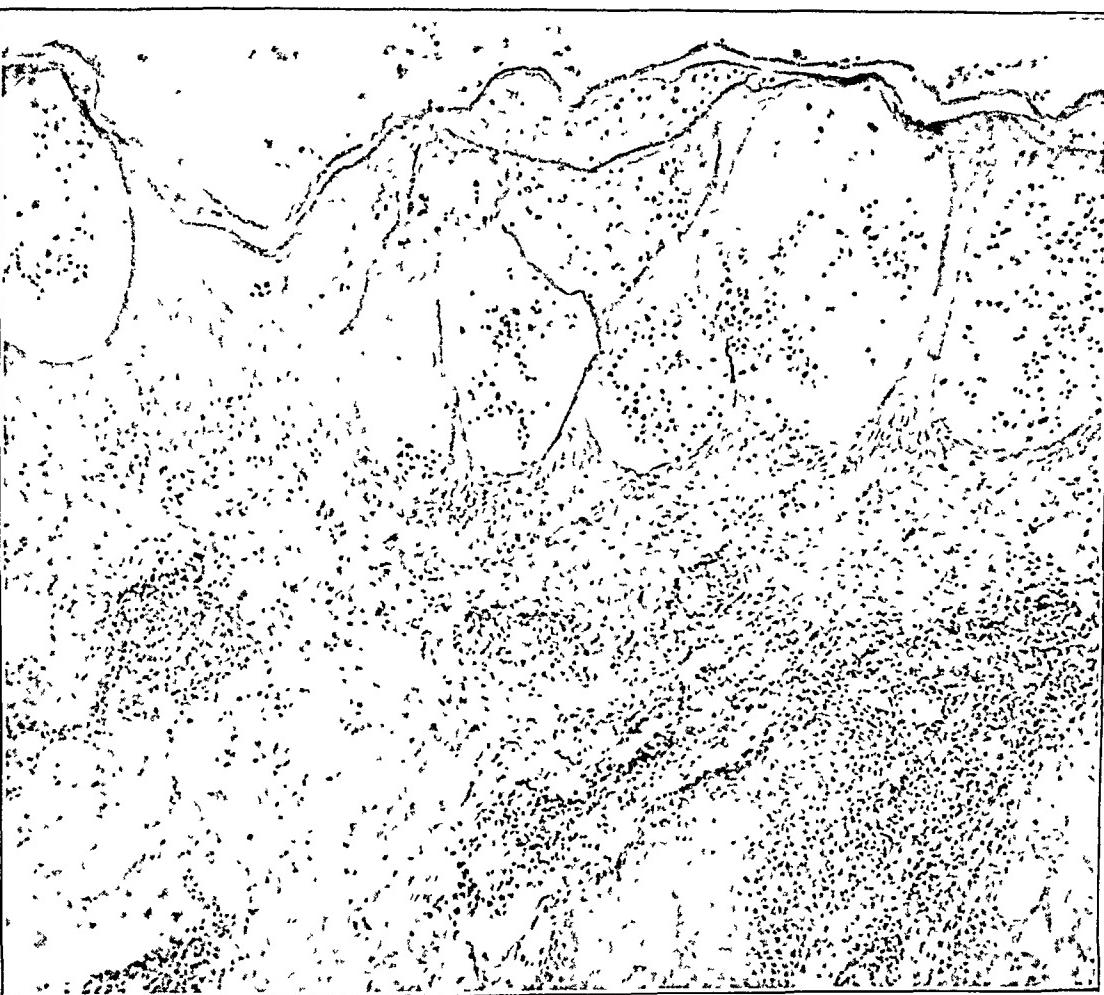


Fig. 4.—Dermatitis venenata rhus, showing vesicular response of contact eczematous dermatitis. ( $\times 60$ .)

present in the lumen of a blood vessel or about it. There is some interstitial edema in the upper part of the cutis. The epidermis may be normal or slightly acanthotic. It shows some intercellular edema. Within the epidermis there are small and large intraepidermic vesicles. Some prickle cells in the subcorneal zone may show edematous degeneration.

In necrotic response (fig. 3) the following changes are seen microscopically. The cutis presents the same picture as is seen in the vesicular response. The interstitial edema, however, is more pronounced. There may also be edema of the collagen bundles. The cellular reaction about the vessels is scant. The epidermis is necrotic. This zone may be localized or it may be extensive. This form of

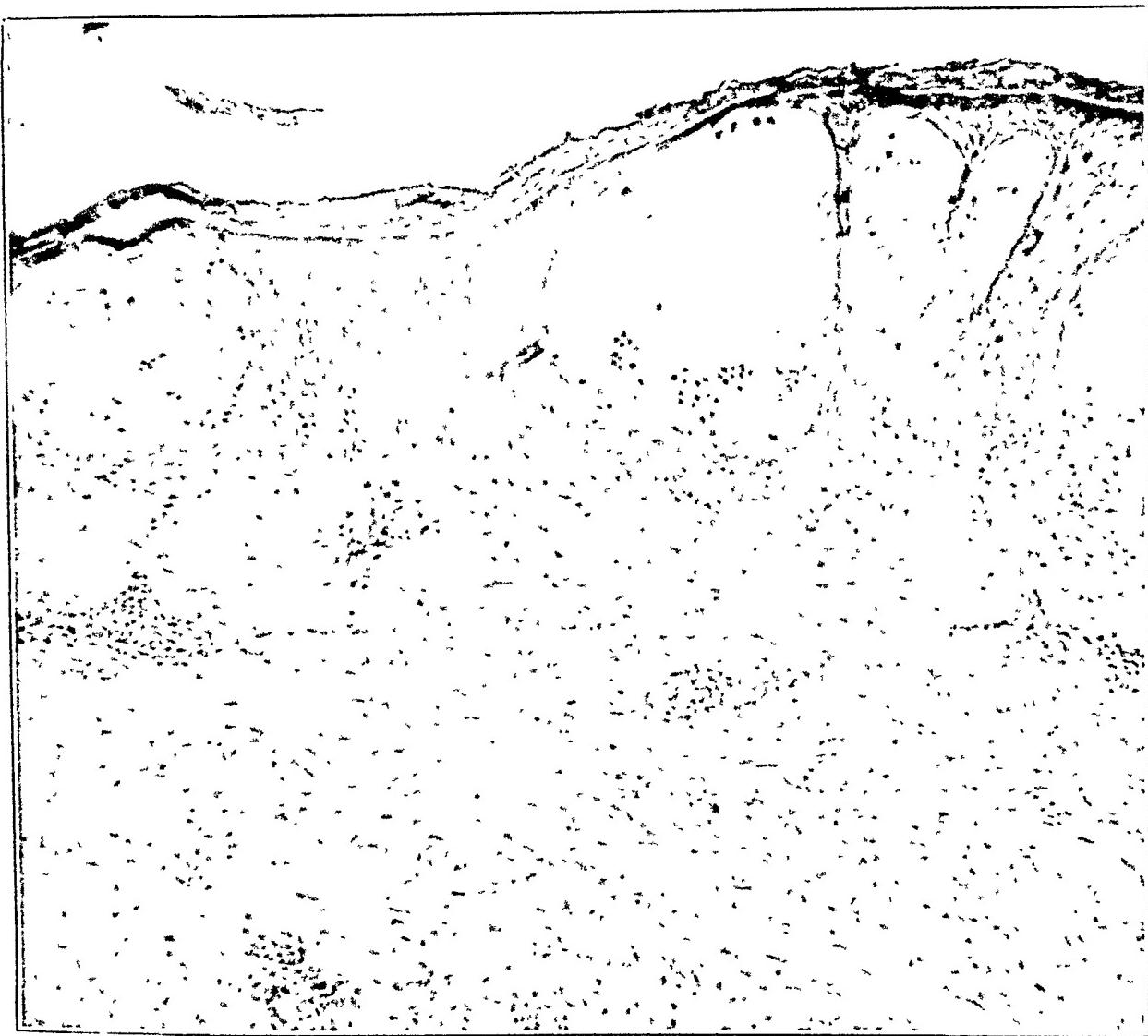


Fig. 5.—Recurrent contact eczematous dermatitis (cause unknown). ( $\times 60.$ )

response was discussed by Sulzberger and his co-workers, who first distinguished it clearly from the allergic contact reaction.<sup>5</sup>

In chronic contact dermatitis time becomes an important factor. There may be repeated exposures to the contact allergen or irritant. Histologically the changes in the cutis are similar to those seen in acute contact dermatitis. The perivascular inflammatory reaction may be more decided, and the epidermis shows some acanthosis. The vesicles may be intraepidermic, subcorneal or even corneal in location.

5. Footnote 2b p. 175.

## REPORT OF CASES

CASE 1.—R. R., aged 36 years, had erythematovesicular patches about the right eye, on the left cheek and forearms and around the umbilicus for ten days. Lesions later broke out on the thighs. The clinical diagnosis was dermatitis venenata rhus. A biopsy specimen was taken from the left forearm on the tenth day of the eruption. The section (fig. 4) showed dilated blood vessels of the upper and middle layers of the cutis. They were surrounded by a perivascular infiltration

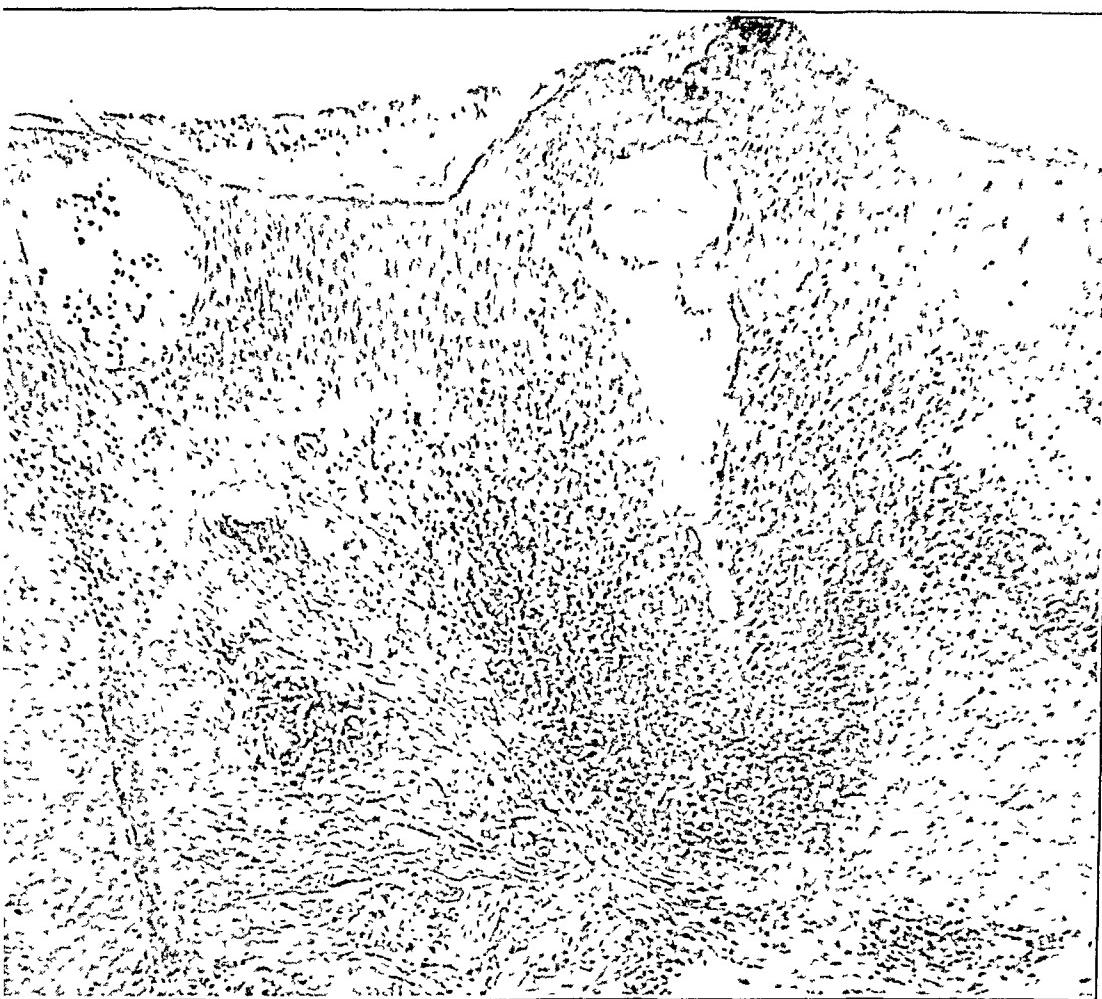


Fig. 6.—Recurrent contact eczematous dermatitis (cause unknown). This slide shows, in addition to the usual intraepidermic vesicles, a vesicle in the intraepidermic portion of the sweat duct with superficial necrosis above it. ( $\times 60$ .)

of small round and wandering connective tissue cells. An occasional leukocyte was seen in the lumen of a blood vessel. There was moderate interstitial edema throughout the upper layer of the cutis.

The epidermis was irregular and slightly acanthotic. Some intercellular edema and decided vesicular formation were present. In some areas the cells of the epidermis in the subcorneal zone showed edematous degeneration. Many of the vesicles were large and extended from the subcorneal zone down two thirds of

the thickness of the epidermis. These vesicles contained fluid, cellular debris and leukocytes. The histologic diagnosis was contact eczematous dermatitis.

CASE 2.—M. W., aged 66 years, had a recurrent eruption of vesicular patches on the volar and dorsal aspects of both hands for many years. The present attack had lasted three weeks. The clinical diagnosis was contact eczematous dermatitis, cause unknown. A biopsy specimen (fig. 5) taken from the dorsum of the hand revealed changes in the cutis similar to those illustrated in figure 4 of the previous case history. The epidermis was slightly acanthotic. It had some



Fig. 7.—This slide of contact eczematous dermatitis shows the vesicle within the intraepidermic portion of the sweat duct. No other vesicles were seen. ( $\times 60$ )

interstitial edema, large intraepidermic vesicles containing fluid, cellular debris and only an occasional leukocyte. The histologic diagnosis was contact eczematous dermatitis.

CASE 3.—D. P., aged 48 years, had a recurrent eruption on the forearms and legs for the past five years. It consisted of ill defined erythematous, scaly and vesicular patches. The clinical diagnosis was recurrent contact eczematous dermatitis. A biopsy specimen (fig. 6) from a patch on the right wrist, which was of

only several days' duration, revealed dilated superficial blood vessels, with a perivascular inflammatory reaction of small round cells and wandering connective tissue cells. There was interstitial edema with parenchymatous edema of the collagen bundles. Many of the collagen bundles showed vacuolization. The epidermis showed slight acanthosis. There was considerable intercellular edema with many large intraepidermic vesicles. These vesicles contained fluid, degenerated epithelial cells and an occasional leukocyte. In the center of the slide, one vesicle was within the intraepidermic portion of the sweat duct. Above this

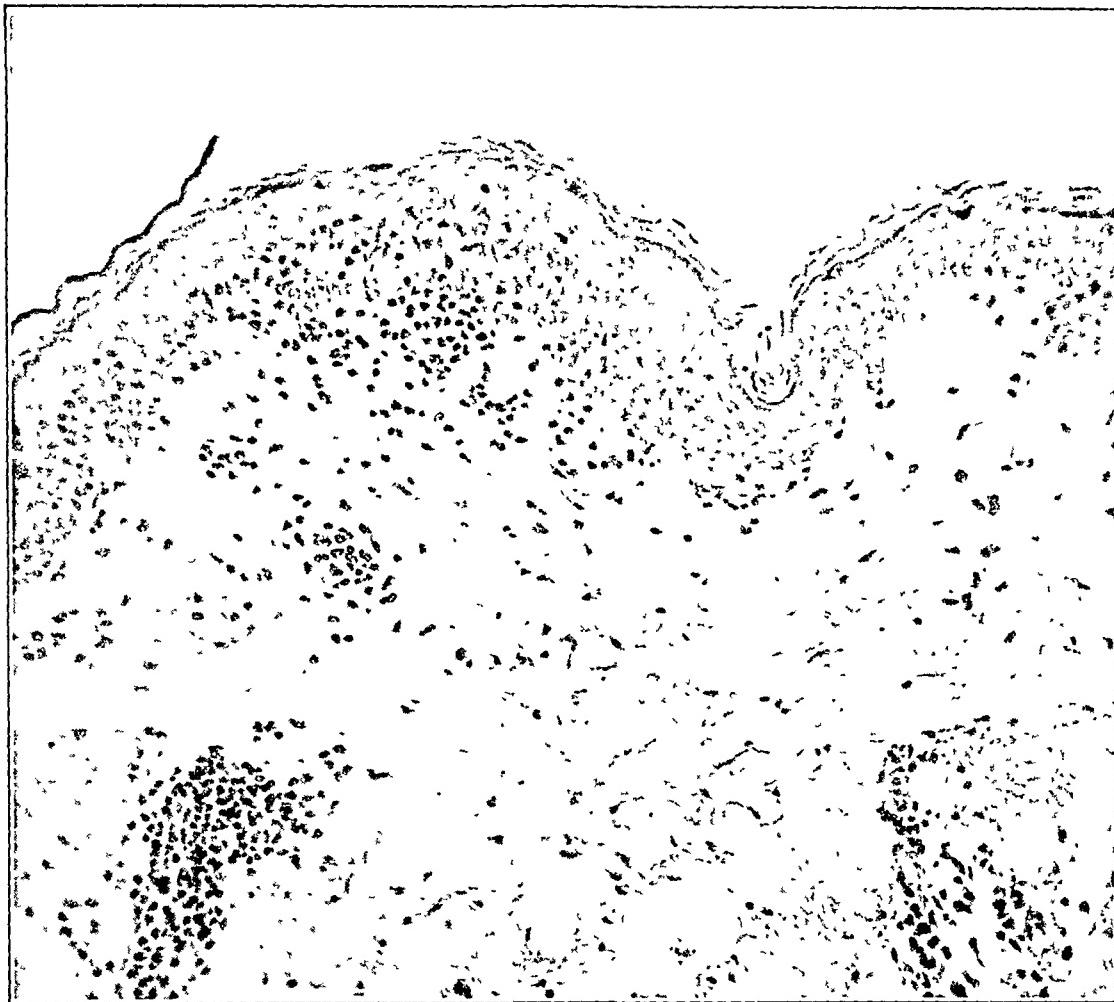


Fig. 8.—Reaction in a patch test with "metaphedrine" (metaphen in epinephrine) in oil (Abbott Laboratories). In forty-eight hours only the edematous degeneration of a few epidermal cells were seen. The cutis shows a superficial type of simple inflammatory reaction. ( $\times 100$ .)

vesicle there was an area of necrosis. The histologic diagnosis was contact eczematous dermatitis of the vesicular and necrotic type.

CASE 4.—J. M., a shoemaker, aged 51 years, broke his forearm. A plaster cast, applied at the time of the injury nine weeks prior to this examination, was still in place. For the last ten days an eruption had appeared under the lower end of the cast. This eruption was composed of discrete vesicles, papules and

pustules. Four days before his appearance at the office, this eruption had become generalized with lesions on the thighs, legs and neck. The clinical diagnosis was contact eczematous dermatitis with "id" reaction.

Microscopic examination (fig. 7) revealed dilatation of the superficial vessels, with a scant perivascular inflammatory reaction, and some interstitial edema of the cutis. The epidermis showed only a vesicle in the intraepidermic portion of the sweat duct, and this vesicle was filled with cellular debris and fluid. The histologic diagnosis was dyshidrotic type of vesicle.

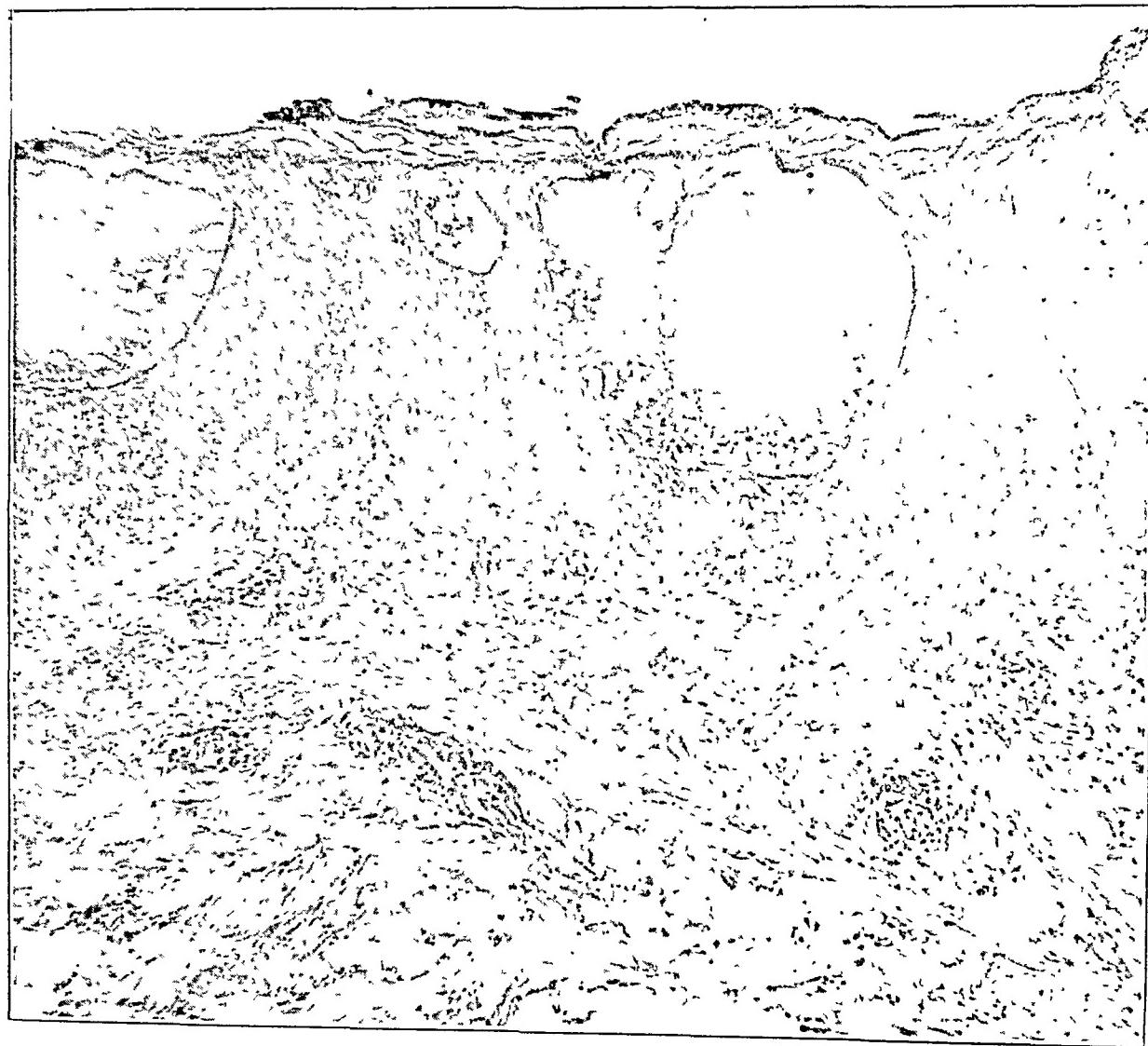


Fig. 9.—Reaction in a patch test with "clairoil" hair dye. This slide shows intense vesicular type of response of contact eczematous dermatitis.

#### STUDY OF REACTIONS IN PATCH TESTS

The following histologic reports are of patients who had positive reactions in patch tests. These tests were made on patients suffering from contact eczematous dermatitis in whom offending allergens or irritants were isolated. The offending agent was applied to the upper anterior aspect of the arm for a period of forty-eight hours, after which

a reading was made. If the reaction was positive, a biopsy specimen was taken. Each area was observed again after another interval of forty-eight hours.

CASE 5.—H. S., aged 35 years, was seen in 1935 and again in 1944 for a similar eruption on the upper lip below the anterior nares. Examination each time revealed an oozing crusted inflammatory patch. The clinical diagnosis was contact eczematous dermatitis.

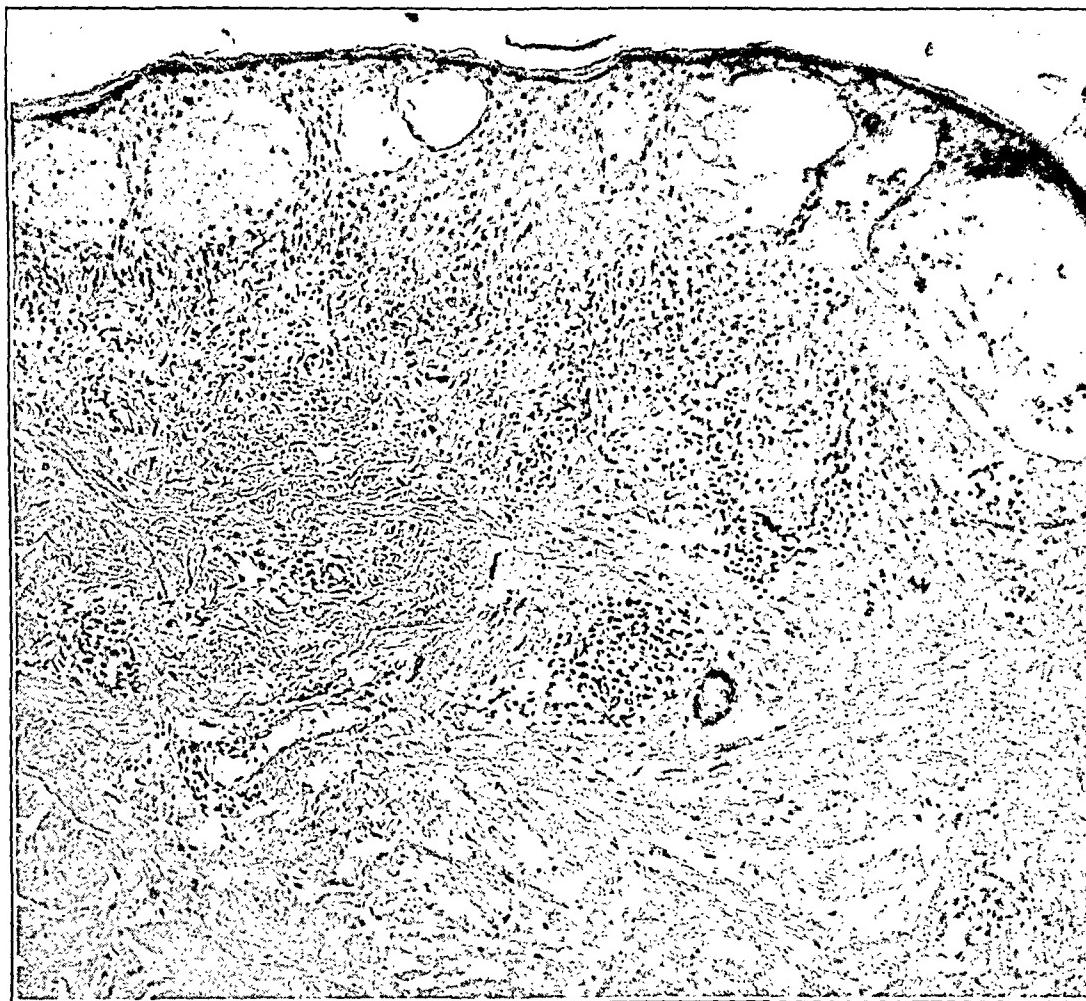


Fig. 10.—Positive reaction in a patch test with turpentine. The histologic picture is that of the vesicular response of contact eczematous dermatitis. ( $\times 60$ .)

Many patch tests were made. A positive reaction manifested by erythema with pinpoint vesicles was obtained in forty-eight hours to the solution of "metaphedrine" (a mixture of metaphen and epinephrine) in oil (Abbott Laboratories). After ninety-six hours the reaction became more apparent.

Microscopic examination (fig. 8) of the biopsy specimen taken in forty-eight hours showed an essentially normal epidermis except for beginning vesicular formation in one area. There were parenchymatous edema of some of the prickle cells, localized intercellular edema and some exocytosis of small round cells. In

of small round cells and wandering connective tissue cells. The entire cutis showed interstitial edema. The epidermis was not acanthotic. It contained many large vesicles and some small ones. The larger vesicles occupied the entire depth of the epidermis. They contained fluid, cellular debris and occasional leukocytes. The histologic diagnosis was contact eczematous dermatitis.

CASE 7.—L. P., a painter aged 52 years, for the past three years had recurrent vesicular patches on the dorsum of the fingers, hands, and volar and dorsal aspects of the forearms. He had desquamation between the toes. The present eruption was of six days' duration. The clinical diagnosis was dermatophytosis of the toes and contact eczematous dermatitis of the hands and forearms.

Positive reactions were obtained in a patch test with a peroxide mixture, the formula of which is a trade secret, and to turpentine. Histologic examination of the reaction to the peroxide mixture (fig. 3) showed congestion of the superficial blood vessels with a scant perivascular inflammatory reaction composed of small round cells and wandering connective tissue cells in the cutis. There was also an occasional leukocyte within the lumen of a blood vessel. The entire epidermis was necrotic. It was separated from the underlying cutis by fluid. The histologic diagnosis was primary irritant type of contact eczematous dermatitis.

Histologic examination of the reaction to turpentine (fig. 10) showed the superficial blood vessels of the cutis to be dilated. There was a moderate perivascular inflammatory reaction of small round cells and wandering connective tissue cells. The upper part of the cutis revealed interstitial edema. There was some infiltration in the subepidermic zone beneath the large vesicles. The epidermis appeared normal, with no acanthosis present. Some intercellular edema was present, with several large and small vesicles. The large vesicles extended from the upper part of the cutis to the basal cell zone. The vesicles contained fluid, cellular debris and occasional leukocytes. The histologic diagnosis was contact eczematous dermatitis.

#### MICROSCOPIC DIFFERENTIAL DIAGNOSES

Contact eczematous dermatitis must be differentiated from (1) eczema, (2) nummular eczema, (3) eczematized neurodermatitis, (4) dermatophytosis and dermatophytide, (5) dyshidrotic type of vesicular lesions, as seen in taenia and dermatophytide, and (7) pustular psoriasis.

*Eczema*.—In all the aforementioned diseases the pathologic changes appear in the upper third of the cutis. In eczema (fig. 11) the infiltration is present about the superficial blood vessels and about the capillaries in the papillary bodies. In contact eczematous dermatitis the infiltration is largely seen about the superficial blood vessels. In eczema the epidermis shows an irregular acanthosis. In contact eczematous dermatitis there is little change from the normal. In eczema there is widespread spongiosis high up in the prickle cell zone, soon followed by decided vesiculation. In contact eczematous dermatitis there is localized intercellular edema, and the involved prickle cells show edematous degeneration. These cells finally rupture with large vesicular formation. In severe contact eczema the entire epidermis may be occupied by many large vesicles.

*Nummular Eczema.*—The picture in nummular eczema (fig. 12) is distinct. First, there are the changes as described in the neurodermatitic reaction.<sup>6</sup> In the neurodermatitic reaction the medial coats of the superficial blood vessels are thickened. There is a perivascular focal cellular reaction of the nonspecific type (small round cells and wandering connective tissue cells). The epidermis shows a somewhat regular acanthosis. In nummular eczema, in addition to these changes, there

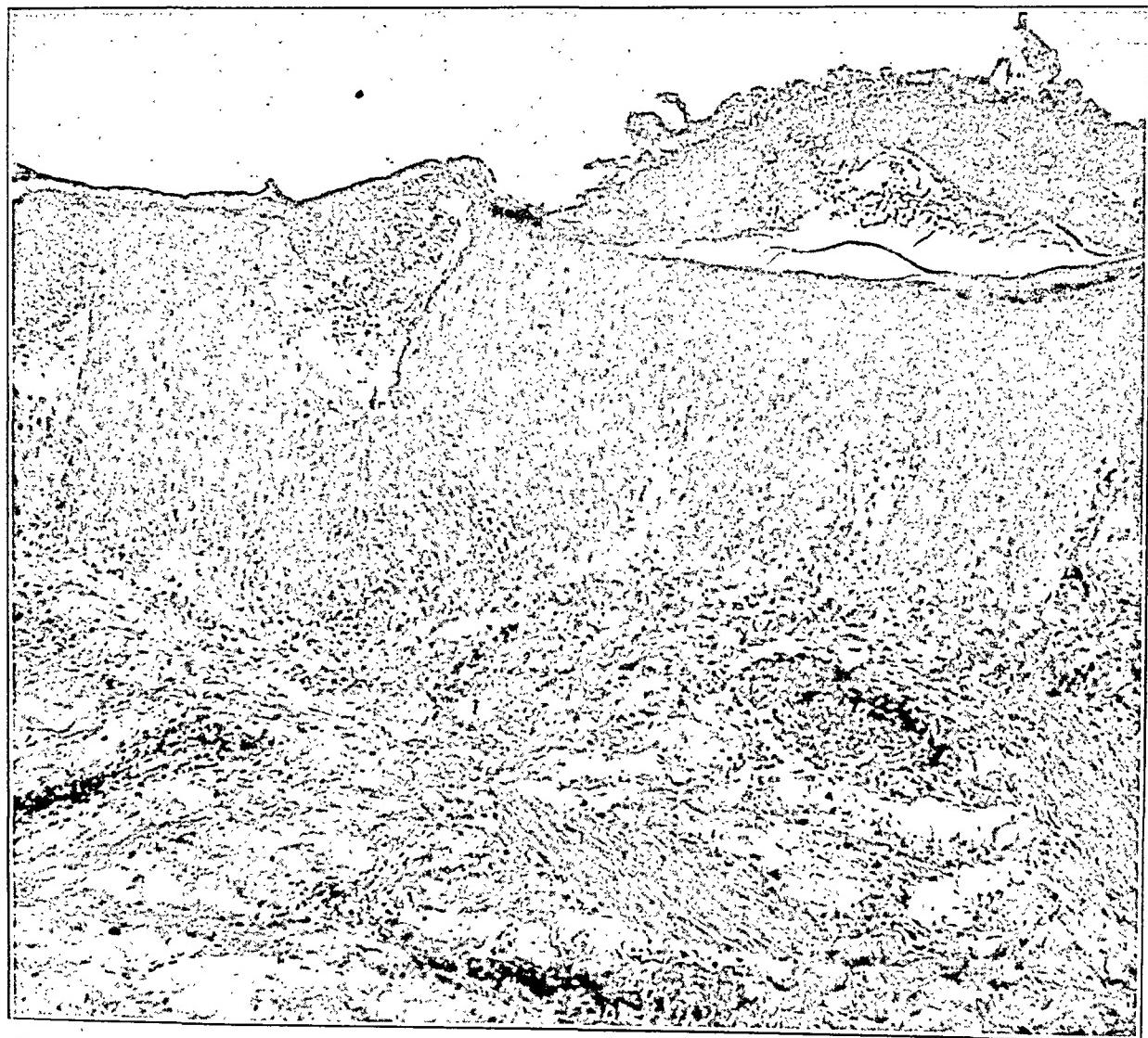


Fig. 12.—Nummular eczema. This slide shows the neurodermatitic reaction plus intraepidermic vesicles containing some cellular elements and leukocytes.

are one or more discrete small or large intraepidermic vesicles. Except for these vesicles, the epidermis is dry. Contact eczematous dermatitis can be differentiated by the lack of the features of the neurodermatitic reaction.

6. Sachs, W.; Miller, C. S., and Gray M.: Neurodermatitic Reaction, Arch. Dermat. & Syph. 54:397 (Oct.) 1946.

*Eczematized Neurodermatitis.*—Eczematized neurodermatitis also presents the picture of the neurodermatitic reaction. Superimposed on this there appear areas of vesiculation high up in the prickle cell zone. Essentially, this picture simulates that of the superficial type of vesiculation of contact eczematous dermatitis superimposed on neurodermatitis.

*Dermatophytosis and Dermatophytide.*—Both dermatophytosis and dermatophytide resemble contact eczematous dermatitis clinically. Histo-

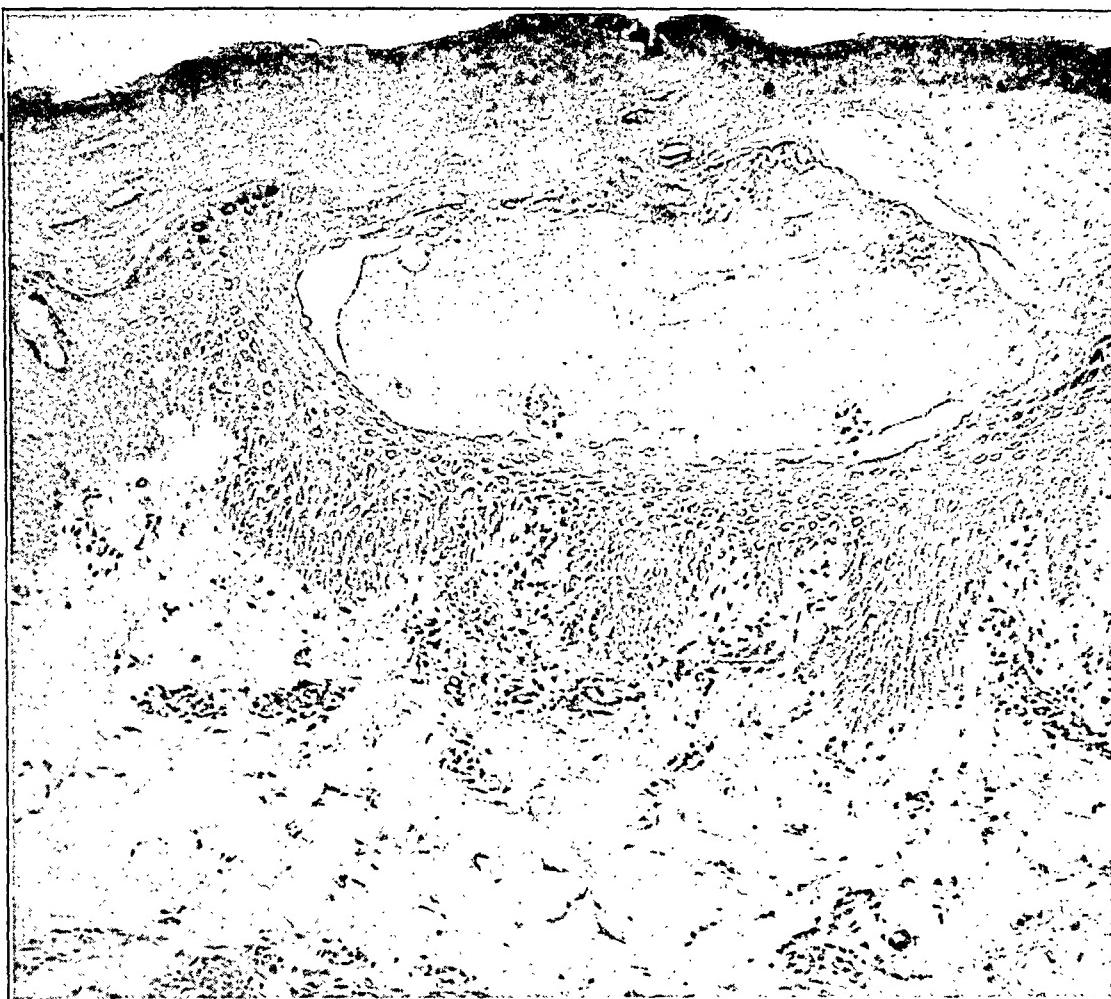


Fig. 13.—Dyshidrotic type of vesicle on the left thumb in a patient with dermatophytosis of the feet and dermatophytide eruption of the palms and fingers. Section shows elements of the sweat duct in the horny zone. ( $\times 60$ .)

logically the resemblance is not so great. The resemblance is closer to the dry stage of eczema, with intercellular edema in some areas of the epidermis. Above these areas, there are patchy zones of parakeratosis. Positive diagnoses of dermatophytosis and dermatophytide cannot be made histologically. Other laboratory tests must be made to confirm such diagnoses.

*Pustular Psoriasis.*—In pustular psoriasis, also (fig. 14), there are large intraepidermic vesicles. These vesicles may appear in any part of the epidermis. They are not associated with the sweat duct system as in true dyshidrosis or in the dyshidrotic type of lesions. The cutis shows changes essentially restricted to the zones beneath the vesicles. Small round cells and wandering connective tissue cells are seen about the capillaries and superficial blood vessels in these areas.

#### COMMENT

Contact eczematous dermatitis presents a definite and characteristic histologic picture by which it can be identified.

The outstanding features of this disease have been described in detail. In brief, they are of two types, one resulting in necrosis of the epidermis and the other resulting in vesicular formation due to edematous degeneration of the prickle cells. The cutis shows congestion of the superficial blood vessels, with a perivascular banal type of inflammatory exudate.

The positive reaction in a patch test is characterized histologically by the same features as any other contact eczematous dermatitis. The severity of the reaction depends on the four factors mentioned.

Contact eczematous dermatitis presents a somewhat different picture in its acute and in its chronic forms. These differences have been described in detail.

There are several other diseases characterized by intraepidermic vesicles seen under the microscope, which must be differentiated from contact eczematous dermatitis. At times the differentiation may be almost impossible. These diseases often put one in a quandary from the standpoint of the clinical diagnosis also. However, in the vast majority of cases differentiation and definite diagnosis are possible. The diseases which so closely simulate one another belong in the group of eczematoid dermatoses.

#### SUMMARY

A histologic study of the disease recognized as contact eczematous dermatitis is presented with its identifying features. With this study is also presented the microscopic observations of positive reactions in patch tests. Points of differentiation of this disease from other members of the group of eczematoid dermatoses are presented.

37-38 One Hundred and Fourth Street.

continued at six hour intervals throughout the duration of the observation. In 1 other case the arsenic and the BAL were given simultaneously. The arsenical used in this experiment was oxophenarsine hydrochloride (mapharsen), employed in a dosage of 10 mg. per 10 pounds (4.5 Kg.) body weight. Daily injections of this drug were given during the period of study. Repeated dark field examinations were performed at frequent intervals each day, until *T. pallidum* could no longer be seen. Arsenical and BAL injections were then discontinued, and 4,000,000 units of crystalline penicillin (40,000 units every three hours) was substituted.

#### REPORT OF CASES

CASE 1.—C. E., a 23 year old Negro, was admitted to the hospital with secondary syphilis of an estimated two months' duration. He presented hypertrophic moist papules of the scrotum and mucous patches of the mouth. *T. pallidum* was found on the dark field, and the serum reaction to the Wassermann and Kline diagnostic tests was 4 plus with a reaction in the titered quantitative test with the Lund technic<sup>3</sup> of 64 units. The observations of the spinal fluid were normal. This man was given 200 mg. of BAL intramuscularly every six hours for eight days. The first dose of BAL was given six hours before arsenical treatment was begun. Oxophenarsine hydrochloride, 0.055 Gm., was given each day. Dark field examinations of material from scrotal lesions showed persistence of active *T. pallidum* for eight days, which then disappeared. Treatment with arsenic and BAL was discontinued and penicillin was administered. During the period of treatment with combined arsenic and BAL there was no appreciable healing of the syphilitic lesions. After the introduction of penicillin the lesions healed. The patient exhibited a grade 1 febrile Herxheimer reaction following penicillin therapy. There were no untoward symptoms referable to the BAL, except for some gluteal tenderness at the site of injection. The only significant observations that could be attributed to BAL were increased leukocyte counts of 18,000 and 13,000, with a slight increase of the polymorphonuclear leukocytes.

CASE 2.—D. A., a 17 year old Negro girl, was hospitalized because of secondary syphilis of two months' duration. There was a generalized maculopapular eruption with condyloma latum on the vulva and perianal region. The condylomas revealed *Treponema pallidum* on dark field examination, and the serologic tests elicited positive reactions to the Wassermann and diagnostic Kline tests. The reaction in the quantitative test was 4 Lund units. The observations on the spinal fluid were normal. This patient was given 200 mg. of BAL intramuscularly every six hours. Six hours after the first injection of BAL, she was given 0.06 Gm. of oxophenarsine hydrochloride, and this was repeated daily. The dark field examination revealed the presence of organisms for eighty-four hours, after which time none were seen. This patient complained of soreness of the gums and a burning sensation of the tongue for about half an hour after each injection of BAL. However, these symptoms were transitory, and no serious difficulty was experienced. There was no alteration of the hemogram. When penicillin therapy was instituted for the comple-

3. Sulkin, S. E., and Gillick, F. G.: Quantitative Kahn Reaction as a Guide to Antisyphilitic Therapy, Am. J. Syph., Gonor. & Ven. Dis. 25:77, 1941.

Based on the assumption that the destruction of spirochetes caused the Herxheimer phenomenon, it must be assumed that there were still many viable spirochetes present at the time penicillin therapy was started.

#### SUMMARY AND CONCLUSIONS

Five patients with acute early syphilis were treated with BAL and oxophenarsine hydrochloride in an attempt clinically to determine whether BAL effected a depressing action on the treponemicidal factor of arsenic.

In 3 of the cases the destruction of *Treponema pallidum* was delayed (long after the time normally required with standard treatment) by the use of BAL. In cases 2 and 5 organisms were still present after three and one-half days of injections of combined arsenic and BAL. In case 1 *T. pallidum* persisted for eight days.

In 1 case the *T. pallidum* quickly disappeared from the lesion following the withholding of one injection of BAL.

In another case, in which BAL and oxophenarsine hydrochloride were given simultaneously, there appeared to be no diminution of the treponemicidal action of oxophenarsine hydrochloride; however, based on the other observations it is thought that this was probably due to the different routes of administration of the two drugs, inasmuch as the arsenical was given intravenously, thus allowing for much faster dissemination.

Adequate doses of BAL have a suppressing effect on the treponemicidal action of arsenic.

Carnegie Medical Building.

# OBSERVATIONS ON SPINAL FLUID IN LYMPHOGRANULOMA VENEREUM

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NEW YORK

THIS article presents the results of examinations of the spinal fluid of 25 men with acute lymphogranuloma venereum; none of the patients had symptoms or signs of involvement of the central nervous system.

In a review of similar studies only a few instances of increase of the white cells and/or protein of the spinal fluid were seen,<sup>1</sup> the spinal fluid in the majority of cases being normal in these respects.<sup>2</sup> Insig-

nificant deviations of the colloidal gold, colloidal benzoin and mastic curves have been recorded.<sup>3</sup> Increased pressure of the spinal fluid was noted in 7 of 9 patients by one author,<sup>4</sup> but was not seen in a single case by others.<sup>5</sup> Peripapillary edema and tortuosity of the blood vessels of the fundus oculi have been observed in cases with and without increased tension of the spinal fluid.<sup>6</sup> While positive Wassermann or

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This investigation was carried out while the author was an officer in the Medical Corps, Army of the United States.

1. (a) Midana, A., and Vercellino, L.: Les altérations du système nerveux central de l'homme dans la poradénite inguinale, Bull. Soc. franç. de dermat. et syph. **41**:161, 1934. (b) Mollaret, P., and Vieuchange, J.: Recherches sur le liquide céphalorachidien dans la forme rectale de la maladie de Nicolas-Favre, Compt. rend. Soc. de biol. **125**:936, 1937.

2. (a) von Haam, E., and D'Aunoy, R.: Infectivity of the Spinal Fluid in Lymphogranuloma Inguinale, J.A.M.A. **106**:1642 (May 9) 1936. (b) Koschucharoff, B.: Ueber das Vorkommen einer Infektion des Zentralnervensystems beim Lymphogranuloma inguinale, Klin. Wchnschr. **17**:876, 1938. (c) Ravaut, P., and Scheikvitch, L.: Lymphogranulomatose inguinale, Bull. et mém. Soc. méd. de Paris **45**:301, 1921. (a) Cruz, H.: El líquido céfalo-raquídeo en el síndrome linfogranulomatoso genito-ano-rectal, Rev. méd. de Chile **65**:49, 1937.

3. Mollaret and Vieuchange.<sup>1b</sup> Koschucharoff.<sup>2b</sup>

4. Kitigawa, K.: Lymphogranulomatosis Inguinalis: Report of Thirty-seven Cases, Especially Clinical Findings of Cerebrospinal Fluid and Eye Ground, Abstracted, J. Orient. Med. **20**:48, 1934.

5. (a) Chaigneau, A., cited by Coutts, W. E.: Lymphogranuloma Inguinale as a General Disease, J. Trop. Med. & Hyg. **39**:13, 1936. (b)- Espildora, C., and Coutts, W. E.: Signos oculares de la linfogranulomatosis venerea, Rev. méd. de Chile **63**:633, 1934.

6. Kitigawa.<sup>4</sup> Espildora and Coutts.<sup>5b</sup>

Meinicke reactions of the spinal fluid were reported in a few cases, close scrutiny of the records revealed that a concomitant syphilitic infection was in all likelihood responsible for these reactions.<sup>4</sup>

The virus of lymphogranuloma venereum was demonstrated in the spinal fluid of 2 of 8 patients with acute lymphogranuloma venereum, and in both cases the fluid was cytologically and chemically normal.<sup>2a</sup> Except for headache, these patients had no symptoms or signs referable to the central nervous system. However, other investigators<sup>3</sup> were unable to induce meningoencephalitis in animals by intracerebral inoculation of spinal fluid from 4 patients with lymphogranuloma venereum.

Positive cutaneous reactions were obtained in proved cases of lymphogranuloma venereum after intracutaneous injection of the spinal fluid from 2 patients who showed only minor increases of the white cells and/or protein. On the other hand, a positive cutaneous reaction was not elicited with completely normal spinal fluid from other patients.<sup>1a</sup>

Low grade meningitis was observed in a woman with suppurative inguinal lymphadenitis and positive reactions to the Frei test.<sup>7</sup> The patient complained only of severe pains in the face and long bones and of headache. No signs of meningitis were present. The spinal fluid was normal in all respects, except for the white cell count which was 11.4 per cubic millimeter.

Fatal meningoencephalitis occurred in a male patient four weeks after the onset of lymphadenitis and three days after incision of a diseased inguinal lymph node.<sup>8</sup> Reactions to the Frei tests were positive. The spinal fluid was clear under tension and contained 136 white cells per cubic millimeter (of which 90 were polymorphonuclear leukocytes and 46 lymphocytes). There were 95 mg. of albumin and 25 mg. of globulin per hundred cubic centimeters. The Wassermann reaction of the spinal fluid was negative, and the colloidal gold curve was 2552533433. Intracutaneous injection of 0.1 cc. of the spinal fluid in 2 patients with proved lymphogranuloma venereum resulted in a positive reaction.

The virus was identified in the spinal fluid of a patient who recovered from meningoencephalitis.<sup>9</sup> The patient was a 25 year old Negro, acutely ill, confused and irrational, with obvious signs of meningitis and only slight bilateral enlargement of the inguinal lymph nodes. The initial lumbar puncture revealed cloudy xanthochromic fluid, containing 4,000 white cells (25 per cent of which were polymorphonuclear

7. Chevallier, P., and Bernard, J.: La méningite chronique atténuee de la poradénite inguinale humaine, Sang **6**:573, 1932.

8. Rajam, R. V.: Report of a Fatal Case of Lymphogranuloma Inguinale from Meningoencephalitis, Brit. J. Ven. Dis. **12**:237, 1936.

9. Sabin, A. B., and Aring, C. D.: Meningoencephalitis in Man Caused by the Virus of Lymphogranuloma Venereum, J.A.M.A. **120**:1376 (Dec. 26) 1942.

of the spinal fluid was recorded and was 620 mg. per hundred cubic centimeters. Despite several relapses of the meningoencephalitis, due to inadequate chemotherapy, the patient finally recovered after prolonged administration of sulfonamide drugs.

#### MATERIAL AND METHOD

Twenty-five men with acute inguinal lymphadenitis were studied. Bilateral inguinal involvement was present in only a single case. Actual nodal suppuration occurred in 12 patients, and these were treated, in addition to sulfonamide drugs given orally, with repeated aspiration of the fluctuant nodes. The duration of the lymphadenitis varied from three to twenty-eight days, and in 10 patients it was longer than fourteen days.

Fever and headache occurred in most of the patients in whom frank suppuration of the lymph nodes developed. Except for headache, which was never severe, there were no symptoms or signs suggesting involvement of the central nervous system.

No patient had a history or clinical evidence of previous disease of the inguinal lymph nodes, and all had positive reactions to the Frei tests with chick embryo antigen ("lygramum"). A complement fixation test of the serum for lymphogranuloma venereum was performed in 7 patients, and reactions were positive in 6 and anticomplementary in 1.<sup>13</sup> Two patients had concomitant active syphilis, 1 seropositive primary and the other secondary. Five additional patients gave a history of adequate treatment for syphilis, and of these 2 had positive Kahn reactions of the blood, 1 a doubtful reaction and 2 negative reactions. The Kahn reactions of the blood were persistently negative in the 18 patients who did not have clinical evidence or a history of syphilis.

A lumbar puncture was performed after confirmation of the clinical diagnosis by a positive reaction to the Frei test. Immediately afterward oral sulfonamide medication was begun. Hemograms, urinalyses and determinations of blood protein were made in many cases and revealed the abnormalities usually associated with the disease. The examination of spinal fluid included a Wassermann test with 0.5 and 1.0 cc. of fluid, a cell count, a Pandy test and a colloidal gold test. In 22 cases an estimation of total protein of the spinal fluid was obtained, and in 11 cases the chloride value and in 13 the sugar content were determined.

Merritt and Fremont-Smith<sup>14</sup> gave the following normal levels per hundred cubic centimeters of spinal fluid: chloride (as sodium

13. The complement fixation tests were performed by the Division of Virus and Rickettsial Diseases, Army Medical School, Washington, D. C.

14. Merritt, H. H., and Fremont-Smith, F.: *The Cerebrospinal Fluid*, Philadelphia, W. B. Saunders Company, 1937.

centimeters. In the other 19 cases in which this examination was made the levels of protein were within normal limits.

The level of chloride was normal in 5 of the 11 patients examined and somewhat reduced in the other 6. In only 1 (case 15) was it considerably lowered, to 546 mg. per hundred cubic centimeters. The determinations of sugar and the colloidal gold curves (except that in case 19) were within the limits of normal.

#### COMMENT

This study revealed few cytologic and chemical alterations of the spinal fluid of 25 men with acute lymphogranuloma venereum. The white cell count of the spinal fluid was normal in all but 1, and the abnormal one was ascribed to concomitant asymptomatic neurosyphilis. In 2 patients there was a moderate increase of the total protein of the fluid, without any other abnormality. The reduced content of chloride of the spinal fluid in 6 of 11 patients is difficult to explain. Reduction of chloride occurs in the spinal fluid in various forms of meningitis, but it is also observed in the absence of meningitis as a reflection of reduced plasma chloride, especially in febrile infectious diseases.

These observations of abnormal values for protein and chloride of the spinal fluid, all of moderate degree, do not constitute sufficient evidence for the predication of invasion of the central nervous system by the virus of lymphogranuloma venereum. On the other hand, it has been shown<sup>2a</sup> that virus invasion of the central nervous system can occur without cytologic or chemical alterations of the spinal fluid and without clinical signs or symptoms. In some instances it appears that such invasion may be the precursor of actual meningoencephalitis. The small recorded incidence of this complication suggests that it is exceedingly rare or that it has been attributed to other causes than the virus of lymphogranuloma venereum. The latter is a distinct possibility especially in women in whom no enlargement of the superficial lymph nodes may be present, and in those men in whom enlargement of the superficial lymph nodes is not striking.<sup>9</sup>

It is interesting to consider the influence of concurrent syphilis and lymphogranuloma venereum on the reactions in laboratory tests, since these diseases not uncommonly coexist. Despite the rather high reported incidence of biologic false positive reactions in serologic tests for syphilis in acute lymphogranuloma venereum,<sup>15</sup> none was encountered in my series among the 18 patients who had no history or clinical evidence of syphilis.

15. Knott, L. W.; Bernstein, L. H. T.; Eagle, H.; Billings, T. E.; Zobel, R. L., and Clark, E. G.: The Differential Diagnosis of Lymphogranuloma Venereum and Chancroid by Laboratory and Skin Tests, Am. J. Syph., Gonor. & Ven. Dis. 27:657, 1943.

## Clinical Notes

### PRIMARY ACTINOMYCOSIS OF THE SKIN Report of a Case

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NEW YORK

*History.*—A white woman, 17 years of age and a resident of New York, who worked with jewelry, in October 1946 noticed a swelling on the line of the left lower jaw. She had at that time a carious molar in the left lower jaw and therefore went to a dentist. He ascribed the swelling on the face to a bad tooth, which he extracted. The wound healed normally, without any complications in the gum or cheek. The swelling on the face did not disappear after the extraction of the tooth, but became larger and began to soften. Two weeks after the extraction the patient went to a hospital in New York and was told that she had an abscess, which was incised and drained. After the drain was removed the lesion



Fig. 1.—Actinomycotic lesion on the line of the left lower jaw.

healed over, but on the fifth day after the incision the lesion again increased in size and again was incised and drained. The patient then received several treatments with ultraviolet rays on the affected area over a three week period, during which time the lesion healed and broke down three times.

Examination on Jan. 11, 1947, revealed a lesion about 2 inches (5.08 cm.) in diameter along the left mandible near the chin. The lesion had a soft fluctuating purplish center and a linear scar from former incisions which was covered by a crust with a small opening in the upper part. Grayish green pus was discharged on slight pressure. There was also a firm infiltration on the periphery and decided tenderness on pressure (fig. 1).

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*Laboratory Data.*—A drop of pus obtained from the discharging sinus and placed on a slide showed the presence of minute whitish granules, which were especially distinctly seen when the drop of pus was covered with a cover slip and examined in transillumination. The granules appeared as round opaque bodies in more transparent pus. Such a preparation, examined under the microscope with a medium power dry lens, subdued light and without addition of any chemicals



Fig. 2.—Actinomycotic granule in pus (unstained,  $\times 115$ ).

or staining, revealed a diagnostically characteristic picture of actinomycosis. The central amorphous mass of the granule was surrounded on the periphery by a palisade-like row of radiating refractile clublike bodies. A similar preparation stained by Gram's method revealed the presence of fine-branching filaments, less than 1 micron wide, which were gram-positive and were seen distinctly only with an oil immersion lens and magnifications of about one thousand times. The filaments

were scattered irregularly in the central part of the granule. They assumed a more radial disposition on the periphery of the granule where they were surrounded by the gram-negative substance of the clubs. Many filaments were broken into elongated segments or minute spherical bodies resembling bacilli and cocci. Some of the filaments presented a beaded appearance, with deeply stained spherical granules inside the filament separated by lightly stained intermediate sections. The picture was diagnostic for actinomycosis (figs. 2, 3 and 4).

On January 16 the patient was seen in consultation with Dr. George M. Lewis, who corroborated the diagnosis of actinomycosis and made valuable suggestions concerning the treatment.

Pus obtained from the lesion was cultured on Brewer's liquid medium at 37 C. and on Sabouraud's medium kept at room temperatures. Plantings on Sabouraud's

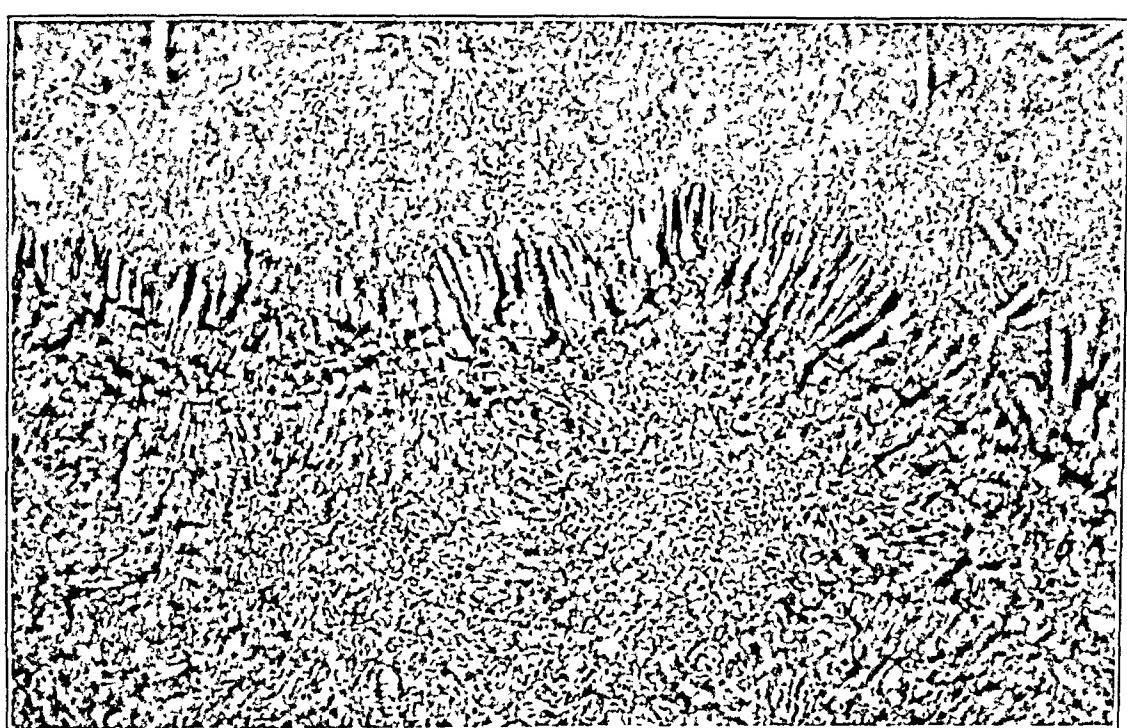


Fig. 3.—Actinomycotic granule in pus, showing the margin consisting of "clubs" (unstained,  $\times 590$ ).

medium remained sterile. Tubes with Brewer's medium showed the growth in the form of white flakes near the bottom of the tube. A microscopic preparation of the flakes, stained by Gram's method, showed gram-positive branched filaments resembling those seen in the pus. There were also numerous gram-negative bacilli and cocci in the smear, so that the results of cultures should be considered doubtful.

*Treatment.*—The patient was admitted to Bellevue Hospital on January 17. General examination revealed nothing essentially abnormal. Dental roentgenographic examination revealed some changes in the right upper and lower premolars, but showed no pathologic changes related to the lesion on the face. The patient's Wassermann reaction of the blood was negative. Examination of the urine and a blood count gave normal results. The treatment began with a course of penicillin

or infiltration around it. At the end of May information was received from the patient's family physician that she was in perfect health.

#### COMMENT

This case was obviously one of primary actinomycosis of the skin and subcutaneous tissue, without any evidence of involvement of deeper parts. The portal of entry of fungi was in all probability the carious molar in the left lower jaw. Many observations indicate that the coexistence of a carious tooth with actinomycosis of the corresponding part of the face or neck is not a simple coincidence. Careful mycologic studies have shown that pathogenic actinomycetes can be present in and around carious teeth in normal persons for a long time without causing any anatomic changes. Fungi can be carried by lymphatic vessels from the gums into the skin. Probably because of the increased sensitivity of the tissues or the increased virulence of the parasites, the pathologic process develops. The primary source of infection in this case, as in many others, remains obscure. Although the cultures failed to produce pure colonies of the fungus, the available clinical and laboratory data suggested strongly that the parasite was *Actinomyces bovis*. Observers have agreed that the vegetative materials and animals are the probable sources of infection. This theory explains the prevalence of actinomycosis in rural districts and among agricultural workers. My patient lived in a city, and her occupation was not a predisposing factor.

The clinical appearance of the lesion simulated a simple abscess, and the true nature of the disease was not recognized for a long time. As soon, however, as the possibility of actinomycosis was considered the diagnosis was easily established. In many cases of this disease, it has been difficult or even impossible to obtain the characteristic granules for a laboratory examination. In this case almost every drop of pus taken before the beginning of treatment contained granules with abundant fungi.

The efficacy of penicillin in the treatment of actinomycosis has been proved in many cases of cutaneous and internal involvement. This drug is the latest addition to the former armamentarium consisting of iodides, thymol, sulfonamide drugs, surgical excision and roentgen rays. According to the "Manual of Clinical Mycology"<sup>1</sup> penicillin is effective in actinomycosis. Clinical improvement may appear in a few days after the beginning of the treatment, and the improvement is more rapid than with the sulfonamide drugs.

Marginson<sup>2</sup> successfully treated with penicillin 5 patients with actinomycosis. Four patients with the inframandibular type of actino-

1. Conant, N. F.; Martin, D. S.; Smith, D. T.; Baker, R. D., and Callaway, J. L.: *Manual of Clinical Mycology*, Philadelphia, W. B. Saunders Company, 1944.

2. Marginson, W. J.: *The Clinical Use of Penicillin in Dermatology*, South. M. J. 38:320 (May) 1945.

mycosis were clinically cured and showed no activity eight months after completion of parenteral treatment with penicillin. The fifth patient, who was gravely ill with involvement of internal organs at the beginning of the treatment, was clinically cured with a total dosage of 8,170,000 units of penicillin.

Hendrickson and Lehman<sup>3</sup> achieved good results with penicillin in 2 cases of the cervicofacial type. One patient received the drug partly by continuous intravenous drip and partly by intramuscular injections, with two injections directly into the lesion. The total dosage was 2,000,000 units. The second patient received penicillin by continuous intravenous drip and intramuscular injections, to a total dosage of 1,500,000 units. These authors recommended intensive treatment with penicillin, without immediate surgical drainage. They considered surgical treatment indicated only when fungi prove resistant to penicillin by laboratory test or when the clinical trial with penicillin fails.

McCrea, Steven and Williams<sup>4</sup> obtained an apparent clinical cure in 1 case of cervical actinomycosis with a course of penicillin which consisted of an initial intramuscular injection of 120,000 units followed by 80,000 units every four hours until a total dosage of 7,000,000 units was reached.

Hamilton and Kirkpatrick<sup>5</sup> obtained cures in 2 cases of the cervicofacial type by intramuscular injections of penicillin every three hours. The total dosage was in 1 case 5,800,000 units and in the second case 5,200,000 units.

Decker<sup>6</sup> observed excellent results in 1 case of thoracic actinomycosis. Penicillin was injected intrapleurally and intramuscularly to a total dosage of 15,000,000 units. This author considered penicillin the most useful drug for actinomycosis anywhere in the body.

Romansky<sup>7</sup> treated 2 patients (1 with actinomycosis of the cervical type, the other with a pulmonary lesion) with intramuscular injections of 300,000 units of penicillin in yellow wax and peanut oil at twelve hour intervals for thirty days, to a total dosage of 18,000,000 units. Both patients responded well. Six months after treatment there were no evidences of relapse.

3. Hendrickson, G. G., and Lehman, E. P.: Cervicofacial Actinomycosis Successfully Treated by Penicillin Without Surgical Drainage, *J.A.M.A.* **128**:438 (June 9) 1945.

4. McCrea, J. H.; Steven, R. A., and Williams, O. O.: Actinomycotic Infection of the Soft Tissues of the Neck: Apparent Cure Following Large Doses of Penicillin, *J. Lab. & Clin. Med.* **30**:509 (June) 1945.

5. Hamilton, A. J. C., and Kirkpatrick, H. J. R.: Actinomycosis Successfully Treated with Penicillin: Report of Two Cases, *Brit. M. J.* **2**:728 (Nov. 24) 1945.

6. Decker, H. R.: The Treatment of Thoracic Actinomycosis by Penicillin and Sulfonamide Drugs, *J. Thoracic Surg.* **15**:430 (Dec.) 1946.

7. Romansky, M. J.: The Current Status of Calcium Penicillin in Beeswax and Peanut Oil, *Am. J. Med.* **4**:395 (Oct.) 1946.

## SUMMARY

A case of primary actinomycosis of the skin of the face in a young woman is presented. The laboratory data indicated infection with *Actinomyces bovis*. Treatment with penicillin by intramuscular injection of 50,000 units every three hours to a total dosage of 10,000,000 units, followed by roentgen irradiation and administration of iodides, achieved an apparent clinical cure.

Dr. Mark A. Kraft referred the patient; Dr. George M. Lewis and Dr. Louis Tulipan gave advice concerning the treatment, and Dr. Rieva Rosh gave information about the details of radiation therapy.

55 West Forty-Second Street.

ing, and as dermatologists with vision and a genuine desire for the continued development of our special branch of medicine, it seems appropriate that the Tenth International Congress of Dermatology and Syphilology should be held in this country, probably in September 1950, and that preparations for the meeting be started at once. It is hoped that when called on, all American dermatologists will assist to their utmost to make the congress a memorable one.

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## News and Comment

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### GENERAL NEWS

**Application for Space in Scientific Exhibit at Next Annual Session.**—The Scientific Exhibit for the next annual session of the American Medical Association, to be held in Chicago in June 1948, is under the direction of Dr. Francis W. Lynch, 1466 Lowry Medical Arts Building, St. Paul. Those who desire to present an exhibit should write directly to Dr. Lynch for application for space.

and have added 1 of our own. Cutaneous or mucoemembranous lesions were observed in 45 (50 per cent) of the 88 patients.<sup>3</sup> We believe that these facts warrant a review of the subject.

mosis: A Report of Four Cases, Two in Siblings; Histoplasmin Test and Other Diagnostic Procedures, *J. Pediat.* **28**:275 (March) 1946. (j) Moore, M., and Jorstad, L. H.: Histoplasmosis and Its Importance to Otorhinolaryngologists: A Review with Report of a New Case, *Ann. Otol., Rhin. & Laryng.* **52**: 779 (Dec.) 1943. (k) Schultze, cited by Ciferri, R.; Redaelli, P., and Visocchi, V.: The Histoplasmoceae Family, *Mycopathologia* **1**:104, 1938. (l) Schlumberger, H. G., and Service, A. C.: A Case of Histoplasmosis in an Infant with Autopsy, *Am. J. M. Sc.* **207**:230 (Feb.) 1944. (m) Wohlwill, F., and Morais, D.: Histoplasmosis de Darling (1 caso observado em Portugal), *Lisboa méd.* **20**:403, 1943. (n) Woodruff, E., and Castellanos L.: Histoplasmosis, *Rev. mex. de tuberc.* **7**:215 (July-Aug.) 1945. (o) Worgan, D. K.: Histoplasmosis: A Summary of the Known Facts About the Disease; Report of a Case, *Bull. School Med. Univ. Maryland* **30**:69 (Oct.) 1945. (p) Perrin, T. G.: Nota sobre el primer caso de histoplasmosis en México, *Rev. d. Inst. salub. y enferm. trop.* **4**:79 (March) 1943. (q) Iams, A.; Tenen, M. M., and Flanagan, H. F.: Histoplasmosis in Children: Review of the Literature, with Report of a Case, *Am. J. Dis. Child.* **70**:229 (Oct.) 1945.

3. (a) Strong,<sup>2a</sup> (b) Alonso and Cancelo Feijo,<sup>2b</sup> (c) Balina, Herrera, Bosq and Negroni,<sup>2c</sup> (d) Kemper and Bloom,<sup>2g</sup> (e) Worgan,<sup>2o</sup> (f) Perrin,<sup>2p</sup> (g) Iams, Tenen and Flanagan,<sup>2n</sup> (h) Darling, T.: A Protozoon General Infection Producing Pseudotubercles in the Lungs and Focal Necroses in the Liver, Spleen, and Lymph Nodes, *J. A. M. A.* **46**:1283 (April 28) 1906; (i) Histoplasmosis: A Fatal Infectious Disease Resembling Kala-Azar Found Among Natives of Tropical America, *Arch. Int. Med.* **2**:107 (Sept.) 1908. (j) Riehl, G.: Durch pathogene Sprosspilze bedingte Granuloma, *Arch. f. Dermat. u. Syph.* **148**:392, 1925. (k) Shaffer, F. J.; Shaul, J. F., and Mitchell, R. H.: Histoplasmosis of Darling, *J. A. M. A.* **113**:484 (Aug. 5) 1939. (l) Hansmann, G. H., and Schenken, J. R.: A Unique Infection in Man Caused by a New Yeast-like Organism, a Pathogenic Member of the Genus Sepedonium, *Am. J. Path.* **10**:731 (Nov.) 1934. (m) Gunter, W. A., and Lafferty, C.: Histoplasmosis of Darling, *J. M. A. Alabama* **9**:337 (April) 1940. (n) Clemens, H. H., and Barnes, M. L.: Histoplasmosis of Darling, *South. M. J.* **33**:11 (Jan.) 1940. (o) Wade, H. W., cited by Meleney,<sup>3h'</sup> (p) Humphrey, A. A.: Reticuloendothelial Cytomycosis (Histoplasmosis of Darling), *Arch. Int. Med.* **65**:902 (May) 1940. (q) Balina, P. L.; Negroni, P.; Bosq, P., and Herrera, J. A.: Histoplasmosis de Darling, *Rev. argent. dermatosif.* **25**:491, 1941. (r) Anderson, W. A. D.; Michelson, I. D., and Dunn, T. M.: Histoplasmosis in Infancy, *Am. J. Clin. Path.* **11**:344 (April) 1941. (s) Villela, E., and Madureira, P.: Histoplasmosis em criança no estado de Minas Geraes, *Rev. brasil. de biol.* **1**:449 (Dec.) 1941. (t) de Almeida, F., and da Silva Lacaz, C.: Cogumelo de genero *Histoplasma* isolado de lesões de cromomicose: Associacão de fungos nos lesões, *Folia clin. et biol.* **11**:65, 1939. (u) Derry, D. C. L.; Card, W. I.; Wilson, R., and Duncan, J. T.: Histoplasmosis of Darling: Report of Case; Mycological Notes, *Lancet* **1**:224 (Feb. 21) 1942. (v) Palmer, A. E.; Amolsch, A. L., and Shaffer, L. W.: Histoplasmosis with Muco-cutaneous Manifestations, *Arch. Dermat. & Syph.* **45**:912 (May) 1942. (w) Dean, L. W., Jr.: Histoplasmosis of the Larynx, *Arch. Otolaryng.* **36**:390 (Sept.) 1942. (x) Thomas, W. C., and Morehead, R. P.: Histoplasmosis, North Carolina M. J.

familiar only with the parasitic phase of the fungus in man and lower animals, with little evidence available to indicate that the organism leads a saprophytic existence outside the animal body. *H. capsulatum* may be strictly a parasite, with survival of the fungus depending on transmission from one animal host to another, or it may exist primarily as a saprophyte in nature, only on occasion assuming a parasitic role. Although organisms resembling this fungus have been observed in the tissues of mice<sup>6</sup> and the ferret,<sup>7</sup> the dog is the only animal from which *H. capsulatum* has been isolated and specifically identified on the basis of cultural characteristics.<sup>8</sup> From available observations it is difficult to assay the role of animals with respect to man's acquisition of the disease, but the dog as a domestic pet in all probability could serve as a reservoir for the infection. Since *H. capsulatum* may readily be identified in and cultured from the peripheral blood, arthropodan transmission from host to host is not beyond the realm of possibility. The occurrence of 2 cases in siblings reported by McLeod and his associates<sup>21</sup> may be an example of transmission from one brother to the other. Clinical observations of human infections as well as information obtained from experimentally induced infections in laboratory animals indicate that the fungus gains entrance to the body by various routes. Although the pathways of infection followed by *H. capsulatum* have not as yet been clearly traced, the occurrence of localized oral, cutaneous and nasopharyngeal lesions suggests that these sites of involvement may serve as portals of entry. The factors which govern localization in one patient and widespread dissemination in another are not known. It is becoming evident, as more cases are reported from widely separated areas throughout the world, that histoplasmosis has no geographic limitation. The disease occurs in North, Central and South America, Africa, Europe and in some of the islands in the Pacific Ocean. It is impossible to conclude from the examination of the histories of the comparatively small number of cases of histoplasmosis reported in the literature that the disease has any well defined predilection for age, sex, race or occupation.

With the possible exception of a few instances, infections with *H. capsulatum* have been of a generalized malignant type with fatal termination. The question as to the probable occurrence of nonapparent and

6. Sangiorgi, G.: Blastomicosi spontanea nei muridi, *Pathologica* **14**:493, 1922. Shortt, H. E.: The Pathogenicity of Insect Flagellates to Vertebrates with Special Reference to Herpetomonas Ctenocephali, Fantham, Indian J. M. Research **10**:908 (April) 1923.

7. Levine, N. D.; Dunlap, F. L., and Graham, R.: An Intracellular Parasite Encountered in Ferret, Cornell Vet. **28**:249, 1938.

8. DeMonbreun, W. A.: The Dog as a Natural Host for Histoplasma Capsulatum: Case of Histoplasmosis in This Animal, Am. J. Trop. Med. **19**:565 (Nov.) 1939.

reactors decreases in proportion to the increasing distance away from the area of high prevalence. It is apparent from his results that geography plays an important role with respect to the prevalence of sensitivity to histoplasmin. The observations and studies of the foregoing investigators indicate that there is a possibility that infection with *H. capsulatum* is in some way related to the problem of pulmonary calcification in persons with a negative reaction to tuberculin.

One of the most complicated phases of the whole problem is the question of the specificity of histoplasmin. Emmons, Olson and Eldridge<sup>11</sup> clearly demonstrated that cross reactions occur in tests with histoplasmin, blastomycin, coccidioidin and haplosporangin. Guinea pigs infected with *H. capsulatum*, *Blastomyces dermatitidis*, *Coccidioides immitis* and *Haplosporangium parvum* all showed positive reactions when tested with histoplasmin. The investigators also tested a group of 136 hospital patients with histoplasmin, blastomycin and coccidioidin. Of these, 40.4 per cent reacted to histoplasmin, 25.7 per cent to blastomycin, 3.7 per cent to coccidioidin and 25 per cent to both histoplasmin and blastomycin. The 5 patients who reacted to coccidioidin also showed positive reactions in tests with histoplasmin and blastomycin. Emmons and Ashburn<sup>12</sup> previously had presented evidence, on the basis of infections in animals, that cross sensitivity exists between haplosporangin and coccidioidin. Smith, in a personal communication with Christie and Peterson,<sup>2e</sup> reported that Air Force personnel infected with *C. immitis* in San Joaquin Valley, Calif., reacted slightly to haplosporangin and more strongly to coccidioidin. However, when men who came to California from Tennessee and Missouri were tested, it was observed that they reacted more strongly to haplosporangin than to coccidioidin.

It is obvious from the observations and studies which have been made that more evidence will have to be presented before it can be definitely established that an infection with *H. capsulatum* ultimately leads to pulmonary calcification or that sensitivity to histoplasmin is associated with calcification in those with a negative reaction to tuberculin. In view of the frequently noted tendency of fungi to produce cross sensitivity reactions some organism other than *H. capsulatum* may be the cause of pulmonary calcification. If *H. capsulatum* is truly the causative agent involved, the ultimate solution of the problem rests on the isolation of the fungus from persons with a benign form of the disease.

11. Emmons, C. W.; Olson, B. J., and Eldridge, W. W.: Studies of the Role of Fungi in Pulmonary Disease: I. Cross Reactions of Histoplasmin, Pub. Health Rep. **60**:1383 (Nov. 23) 1945.

12. Emmons, C. W., and Ashburn, L. L.: The Isolation of *Haplosporangium Parvum* N. Sp. and *Coccidioides Immitis* from Wild Rodents: Their Relationship to Coccidioidomycosis, Pub. Health Rep. **57**:1715 (Nov. 13) 1942.

1. *Ulcerations and Granulomatous Involvement of the Oral Mucosa.*—There were 28 patients in the group with ulcerations and granulomatous involvement of the oral mucosa. In 10 instances the tongue was involved,<sup>13</sup> in 9 the larynx,<sup>14</sup> in 7 the mouth in general,<sup>15</sup> and in 2 the nasal septum was perforated.<sup>16</sup> *H. capsulatum* was demonstrated in most of these oral lesions either microscopically in sections of biopsy tissue or by culture.

In many instances the lesion of the tongue began as a solitary slightly indurated plaque on the upper surface of the tongue. There was no pain until ulceration occurred. It ultimately involved a large part of the tongue and was deep seated. In some cases the lesion on the tongue was the only apparent evidence of infection, while in others there was extensive involvement throughout the body.

The lesions of the larynx, vocal cords, epiglottis and posterior surface of the tongue were generally described as small discrete nodules, gray in color and somewhat dome shaped. They subsequently ulcerated, with associated pain and ultimate thickening or destruction of the involved organs.

In some patients with extensive systemic involvement, small ulcerated areas developed in the mucous membranes of the oral cavity. These areas were noted particularly a short time before death. In some instances the lesions would undergo involution and new ones would form after a short period of time. Perforation of the nasal septum was observed in an infant of 7 months and in a woman of 25 years.

2. *Papules, Plaques and Punched-Out Ulcers.*—These cutaneous lesions were observed in 11 patients<sup>17</sup> and measured 1 to 2 cm. in diameter. They generally began as papules or small plaques which had annular margins and depressed centers resembling lupoids or

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13. The cases of Boltjes,<sup>2d</sup> Kemper and Bloom,<sup>2g</sup> Hansmann and Schenken,<sup>31</sup> Palmer, Amolsch and Shaffer,<sup>3v</sup> cases A, D, and E (of Parsons) cited by Parsons and Zarafonetis,<sup>1</sup> case H (of Stingily) cited by Parsons and Zarafonetis<sup>1</sup> and the cases of Henderson, Pinkerton and Moore<sup>3g</sup> and Simson and Barnetson.<sup>31</sup>

14. Alonso and Cancelo Freijo.<sup>2b</sup> Balina, Negroni, Bosq and Herrera.<sup>3q</sup> Palmer, Amolsch and Shaffer.<sup>3v</sup> Dean.<sup>3w</sup> Negroni.<sup>3z</sup> Parsons.<sup>3d'</sup> Brown, Havens and Magath.<sup>3f'</sup> Van Pernis, Benson and Holinger.<sup>3j</sup>

15. The cases of Boltjes,<sup>2d</sup> Hansmann and Schenken<sup>31</sup> and Humphrey<sup>3p</sup> and cases A, B and D (of Parsons) cited by Parsons and Zarafonetis<sup>1</sup> and the case of Williams and Cromartie.<sup>3k'</sup>

16. Case B (of Parsons) cited by Parsons and Zarafonetis<sup>1</sup> and the case of Agress and Gray.<sup>3e'</sup>

17. The cases of Darling,<sup>3i</sup> Riehl,<sup>3j</sup> Clemens and Barnes,<sup>3n</sup> Balina, Negroni, Bosq and Herrera,<sup>3q</sup> Palmer, Amolsch and Shaffer,<sup>3v</sup> Negroni,<sup>3z</sup> Hansmann and Schenken<sup>3a'</sup> and cases B and E (of Parsons) cited by Parsons and Zarafonetis<sup>1</sup> and case G (of Steiner) cited by Parsons and Zarafonetis<sup>1</sup> and the case of Agress and Gray.<sup>3e'</sup>

popliteal spaces and gradually involved his entire body during the next thirteen years. The skin was red, thickened and decidedly pruritic, and there was an associated enlargement of the superficial lymph nodes. Three months before death, hard umbilicated papules, 0.5 to 1.0 cm. in diameter, developed all over his body as well as in the tongue and oral mucous membranes. The fungus was observed in the skin and lymph nodes one and a half years before the papules developed. The authors expressed the belief that the infection was present throughout the course of the eruption and was not superimposed on the dermatitis.

The cutaneous lesions reported in patients with histoplasmosis are not sufficiently characteristic to permit one to make a positive diagnosis from the appearance of the involved skin alone. The causative organisms were readily demonstrated by microscopic examination and culture in biopsies from a surprisingly large number and variety of lesions. It is of interest that Schlumberger and Service<sup>21</sup> observed *H. capsulatum* in sections of normal-appearing skin removed at autopsy from a 3 month old child who had died of the disease.

The lesions diagnosed in infants as impetigo are of particular interest. In 1 instance the lesions developed when the child was 4 days of age and persisted until death, ten and one-half months later. Unfortunately, data relating to microscopic or cultural examinations of material obtained from these impetigo-like lesions have never been reported. The discovery of histoplasmosis in a premature infant a few months after birth<sup>22</sup> suggests that the infection may have been acquired in utero.

The generalized pruritic eruptions of many years' duration described in patients with enlargement of superficial lymph nodes are indistinguishable from cutaneous involvements associated with lymphoblastomas. Undoubtedly in the past some patients with histoplasmosis and with generalized erythroderma have been given a diagnosis of lymphoblastoma.

#### HISTOPLASMOSIS AS RELATED TO RETICULOENDOTHELIAL DYSCRASIAS

When histoplasmosis is coexistent with another infectious granuloma caused by a specific organism it is usually impossible to determine microscopically which reaction is caused by *H. capsulatum* and which by the coexistent organism. This simultaneous occurrence of another pathogenic organism with the fungus is not rare. The second type of infection is often tuberculosis. Including the case which is presented in this report, there have been 5 instances in which the tubercle bacillus has been isolated in cases of proved histoplasmosis.<sup>19</sup> It is probable

19. Parsons and Zarafonetis.<sup>1</sup> Thomas and Morehead.<sup>3x</sup> Meleney.<sup>3h</sup>

xiphoid process. Roentgenograms of the chest showed a group of nodes in the midline below the arch of the aorta, but no other abnormalities. Numerous encapsulated yeastlike bodies contained within mononuclear cells were observed in stained smears of tissue removed from the edge of the ulcer of the tongue. A tentative diagnosis of histoplasmosis was made and then definitely confirmed on Jan. 26, 1944, when colonies of *H. capsulatum* were observed in cultures which previously had been inoculated with scrapings of tissue from the ulcer. Sections of the cervical lymph node, removed elsewhere in 1938, were obtained, and, after a long search, a mononuclear cell was seen containing three pale-staining inclusions resembling the organisms observed in the tissue of the tongue.

The patient was admitted to the University Hospital on Jan. 18, 1944 for further investigation.

Laboratory studies gave the following results: The Wassermann and Kahn reactions of the blood were negative. The blood count and urine were essentially normal. The serum protein totaled 12.07 Gm. per hundred cubic centimeters (albumin 4.3 and globulin 7.77). The serum calcium was 8.8 mg. and phosphorus 3.04 mg. per hundred cubic centimeters. Aspirated marrow showed a normal



Fig. 1.—Histoplasmosis of the tongue.

count. *H. capsulatum* was not recovered in cultures of the sternal bone marrow or in repeated blood cultures. Several Giemsa-stained thin and thick blood smears were examined, but the yeast phase of the fungus was not observed. Intradermal tests employing histoplasmin, coccidioidin and haplosporangin were performed on January 24, but only equivocal reactions occurred. Microscopic examination ultimately revealed the characteristic yeast cells of the fungus in sections of an extirpated axillary lymph node. However, the fungus did not develop in cultures inoculated with material from this same lymph node. Sputum cultures made on January 27 were likewise negative.

From January 28 to February 11, sulfadiazine was given orally in increasing doses from 4 to 12 Gm. daily, the blood level reaching 15.8 mg. per hundred cubic centimeters on February 11. On February 4, scrapings of the lesion of the tongue again were taken and positive cultures were still obtained. In mice inoculated with some of this same material a widespread infection with *H. capsulatum* developed. There was no improvement in the appearance of the ulcer of the tongue, nor was there any reduction in the temperature range of 36 to 39 C.

were large numbers of macrophages, many of which contained masses of yeast cells. No actual caseation and no formation of tubercles were observed. The pleomorphism of the macrophages was not prominent, and there was no cellular proliferation which even vaguely suggested neoplastic processes. An occasional Langhans giant cell was encountered which was heavily parasitized. The diagnosis was chronic ulcer of the tongue containing *H. capsulatum*.

*Biopsy of Axillary Lymph Node* (January 1944).—The greater portion of the axillary lymph node was completely replaced by caseous material having all the

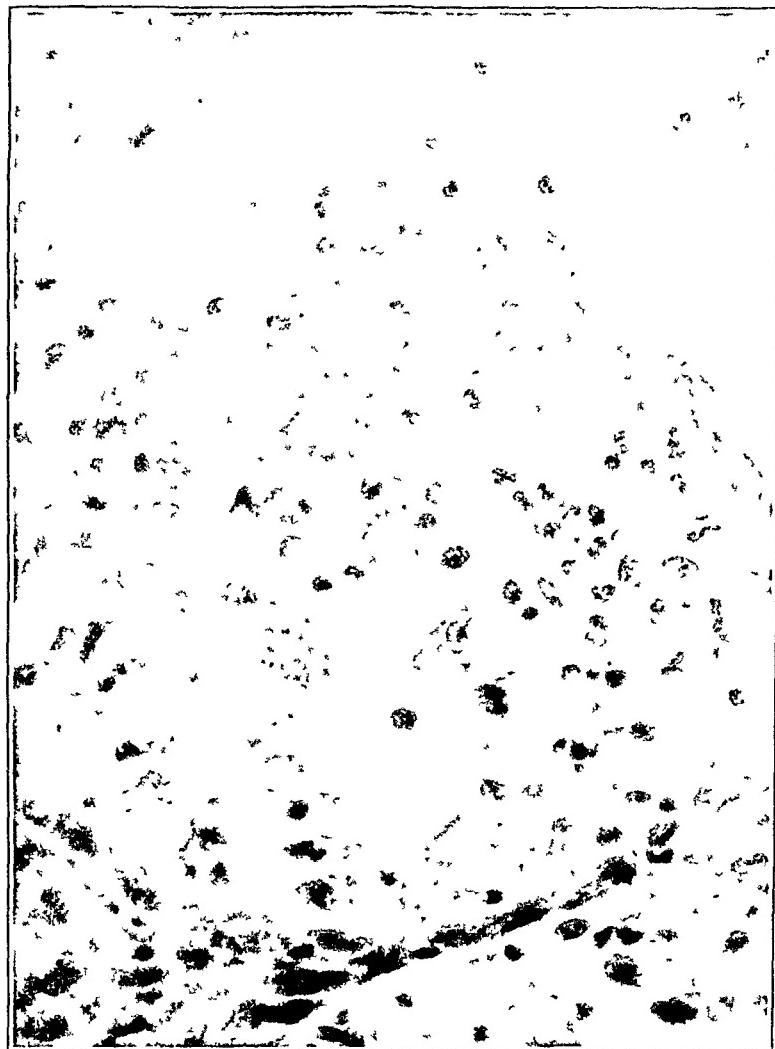


Fig 2.—*Histoplasma capsulatum* in a section of the tongue  $\times 500$

morphologic characteristics of an old tuberculous focus. In one area, the node had not been involved by this apparent tuberculous reaction, but instead showed increased numbers of chronic inflammatory cells with a definite predominance of the macrophage type. Many of these macrophages appeared to be rather foamy, with some tendency to lie in syncytial masses, but no actual formation of tubercles was present. Caseation and necrosis were absent in this portion of the lymph node, and no Langhans giant cells were encountered. Some fibrosis was present, and in

nodules 1 to 5 mm. in diameter, similar in appearance to the nodules seen in the lungs. The spleen weighed 920 Gm. and was grossly not remarkable except for the presence of similar nodules. The intestinal tract was normal except for two grossly caseous mesenteric lymph nodes 1 cm. in diameter. The adrenal glands had no gross abnormalities. The kidneys weighed 240 Gm. each and were grossly normal except for the tubercle-like structures present in infrequent numbers. The brain weighed 1,500 Gm. and grossly presented no abnormalities.

Microscopically all of the small tubercle-like structures had the architecture of a typical early tubercle. In this structure, the Langhans giant cells were not abundant and were often poorly formed. The tubercle was not well walled off, and it appeared to be moderately exudative. The macrophage reaction, although present, was obscured by the exudate, which centrally was not of the classic caseous type but had quite a few degenerated nuclear fragments and scattered granulocytes. There had been little conglomeration of any of these structures. Acid-fast stains revealed tubercle bacilli. In the lymph nodes from the autopsy the tuberculous reaction appeared more mature, with well defined surrounding fibrosis and fully mature Langhans giant cells. Near these older areas of tuberculous reaction a few early tubercles of the miliary type were encountered, but no yeast cells of *H. capsulatum* were observed. There was no suggestion of histoplasmosis in any of the sections of tissues obtained at autopsy, except in the tongue, and these sections showed a process identical with that described in the biopsy taken in December 1943.

Besides the tuberculous reaction already described, the liver and spleen showed still another local type of reaction which was neoplastic. These foci were decidedly cellular and were microscopically not inflammatory in type. No caseation was seen here, acid-fast bacteria were not present and Langhans' giant cells were absent. There were closely packed nonencapsulated sheets of cells, which were often multinucleated and which showed a great deal of pleomorphism and active mitotic proliferation. Individual cells were large and had a lightly eosinophilic ill defined, rather abundant cytoplasm, which often contained more than one nucleus. The nuclei were prominent and vesicular in type and had a clearcut but not heavy nuclear membrane. Often a central, rather large and occasionally eosinophilic nucleolus was seen. Besides these prominent giant cell forms having as many as a dozen nuclei, there was seen a background of reticuloendothelial type of cell and scattered typical lymphocytes. Fibrosis was not particularly prominent. Eosinophils were not seen, but scattered polynuclear granulocytes and plasma cells were in evidence. This clearly neoplastic process was composed of malignant derivatives of the reticuloendothelial system. It could be classified as a type of primitive "stem cell" lymphosarcoma. However, it is believed that the term Hodgkin's sarcoma best fits this pleomorphic picture. The neoplastic tissue was seen only in the liver and spleen. The adrenal glands were microscopically not remarkable, and the tissue of the brain was within normal limits. *H. capsulatum* was recovered in cultures of the cardiac blood, but not in cultures of spleen and liver pulp, bile, urine and fluids aspirated from the peritoneal, pleural and pericardial activities.

The final pathologic diagnosis was: (1) histoplasmosis of the tongue with extension to the cervical and axillary lymph nodes and terminal invasion of the blood stream, (2) malignant lymphoma (probably best classified as a Hodgkin disease type) involving cervical lymph nodes, spleen and liver and (3) old tuberculosis of the pulmonary and hilar lymph nodes with subacute miliary dissemination to lungs, liver, spleen, lymph nodes and kidneys.

were made at five day intervals. An abundant staphylococcus-like growth was obtained, and microscopic examination showed small budding oval yeastlike bodies, closely resembling the parasitic forms seen in tissues. Although the yeast cells predominated in such cultures, a small amount of hyphal growth was invariably present. Unsealed blood slants maintained at room temperature developed the characteristic aerial mycelial growth.

Necrotic tissue obtained by gently scraping the borders of the lesion on the tongue was ground in a mortar with isotonic solution of sodium chloride and sand. The resulting suspension was inoculated intraperitoneally into 3 mice. One of the mice died after seventy-nine days, the second was killed after eighty-two days and the third died ninety-two days after inoculation. Postmortem examinations were performed, and greatly enlarged livers and spleens were observed in all the animals. Blood plate cultures, Giemsa-stained impression smears and histologic sections of these organs revealed that an overwhelming infection with *H. capsulatum* had developed in the mice.

Two types of antigens for use in the complement fixation test were prepared with the fungus isolated from the patient, one employing the mycelial phase and the other the yeast phase of the organism. For the preparation of the mycelial phase antigen, it was discovered, after the trial inoculation of several types of liquid mediums, that the beef heart hormone broth produced the most rapid and luxuriant growth of the fungus. Flasks with a capacity of 500 cc. containing 200 cc. of the broth were inoculated with 0.5 cc. of a saline suspension of yeast phase growth scraped from blood slant cultures, which had been sealed with "parafilm" and incubated at 37 C. The inoculated flasks were kept at room temperature for forty-six days. Phenol was then added to give a final concentration of 0.5 per cent, and the flasks were incubated at 37 C. for forty-eight hours. The contents of the flasks were first filtered through paper and then run through a Seitz filter. The filtrate was bottled, tested for sterility and stored in the refrigerator. The yeast phase antigen was prepared by inoculating Roux flasks (with metal or plastic screw tops) containing beef heart hormone agar with 1 cc. of a saline suspension of yeast phase growth from a sealed blood slant culture. The flasks were incubated for eight days at 37 C., and all those showing an abundance of mycelial growth were discarded. The growth in each flask was washed off the agar surface with 25 cc. of buffered saline suspension ( $\text{pH}$  7) containing 0.5 per cent phenol. Sterile glass beads dropped into the flasks greatly facilitated removal of the growth. The phenol saline suspension of the yeast phase growth was incubated at 37 C. for forty-eight hours, transferred to large tubes and centrifugalized. The clear supernatant fluid was filtered through a Seitz filter, bottled, tested for sterility and stored in the refrigerator. The procedures followed for the preparation of the intradermal test antigen were identical with those employed in the preparation of the mycelial phase complement fixation antigen noted previously. However, the beef heart hormone broth cultures in this instance were incubated at a temperature of 28 C. and phenol added at the end of an incubation period of sixteen days.

Quantitative complement fixation tests were performed with the patient's serum, employing both the mycelial phase and yeast phase antigens. The results obtained follow:

Serum dilutions .....	1:2	1:4	1:8	1:16	1:32
Yeast phase antigen diluted 1:4.....	++++	++++	+++	+++	++
Mycelial phase antigen diluted 1:4....	++++	++	++	+	-

To eliminate the possibility of false reactions caused by the culture medium, control tests were performed with the phenolized beef heart hormone broth. The reactions were negative.

The cutaneous sensitivity of the patient was tested by the intradermal injection of 0.1 cc. of a 1 to 100 dilution of each of the following antigens: three lots of histoplasmin designated as 1, 2 and 3, one of coccidioidin and one of haplosporangin.<sup>24</sup> There were no immediate reactions. The accompanying table shows the reactions observed in twenty-four and forty-eight hours:

*Cutaneous Sensitivity to Intradermal Injection of Antigens*

Antigen	Area Affected (Mm.)	
	After 24 Hours	After 48 Hours
Histoplasmin 1.....	8 *	8 *
Histoplasmin 2.....	10 †	10 †
		10 *
Histoplasmin 3.....	6 *	6 *
Coccidioidin.....	6 †	5 *
Haplosporangin.....	12 †	8 †

\* Erythema.

† Edema.

If only those tests were considered positive which showed an area of edema 5 mm. or more in diameter, it will be seen that histoplasmin 2, coccidioidin and haplosporangin elicited positive reactions. In those instances in which erythema occurred without induration the reactions were considered negative.

When antigen prepared from the patient's own strain of *H. capsulatum* became available the patient was tested intradermally with a series of dilutions. To eliminate any possibility of false reactions, control tests were performed with corresponding dilutions of phenolized beef heart hormone broth. At intervals during a twenty day period the patient was tested with 0.1 cc. injections of the 1 to 10,000, 1 to 1,000 and 1 to 100 dilutions of both the antigen and control fluid. In addition undiluted antigen and control fluid were employed. When the reactions were observed after twenty-four and forty-eight hours it was observed that all were negative. However, the undiluted antigen produced an immediate response, although no delayed reaction occurred. The potency of this antigen may be questioned in view of the comparatively short period of incubation which was utilized during its preparation.

Since there are some rather striking similarities between histoplasmosis and visceral leishmaniasis (kala-azar), it was decided to perform Napier's serum test with the patient's serum. This simple test is widely employed in endemic regions for the diagnosis of kala-azar. It is performed by adding 1 drop of commercial formaldehyde to 1 cc. of the patient's serum in a small test tube. A tube containing the same amount of normal serum is used as a control. The tubes are shaken and allowed to stand at room temperature. A positive reaction is obtained if the mixture in the tube becomes solid and opaque within thirty minutes. According to these standards the reaction with our patient's serum was negative since, although solidification occurred in fifteen minutes following the addition of the drop of formaldehyde, the mixture did not become opaque until two hours and fifteen minutes later. The control serum did not solidify or become opaque within twenty-four hours.

24. All of the lots were supplied by Dr. Charles E. Smith of the Stanford Medical School.

Wolff's<sup>25</sup> precipitation test was also performed with the patient's serum. This simple serologic procedure is employed in the diagnosis of malaria and, according to the originator, kala-azar is the only other infection in which positive reactions regularly occur. The test is based on the precipitation of the euglobulin fraction of the serum by buffer solutions. Only two solutions are employed in the test, one a test buffer solution and the other a control solution. The presence of varying amounts of precipitate in the "test" tube indicates a positive reaction. With our patient's serum a definite precipitate formed in the "test" tube, whereas the control tube remained clear.

*Comment.*—The patient had a somewhat benign type of histoplasmosis with involvement of the cervical and axillary lymph nodes and tongue and a terminal invasion of the blood stream. The diagnosis was made by biopsy of the lesion of the tongue five months before death. Death probably was due to disseminated miliary tuberculosis. It is not unlikely that the roentgen ray therapy given to various parts of the body may have contributed to the terminal miliary dissemination of the tuberculous process. A malignant lymphoma, best classified as a variant of Hodgkin's disease, was coexistent.

The clinical appearance of the ulcer on the tongue was suggestive of tuberculosis or syphilis. The initial nodule was firm in consistency and not painful until sometime after ulceration developed. The location of the lesion on the middorsal surface of the tongue was more suggestive of syphilis than tuberculosis. It might have been possible to cure it with larger amounts of roentgen rays.

#### SUMMARY

A study of 88 cases of histoplasmosis reported in the literature reveals that cutaneous or mucomembranous lesions were present in 45, or about half the number. *Histoplasma capsulatum* was observed in a large percentage of these cutaneous lesions.

The cutaneous and mucomembranous lesions described in the reported cases fall into five distinct groups: (1) ulceration and granulomatous involvement of the oral mucosa, (2) papules, plaques and punched-out ulcers, (3) purpuric lesions, (4) abscesses, furunculoid and impetiginized areas and (5) local or generalized dermatitis.

An additional case of histoplasmosis is reported in a man in whom an ulcer of the tongue developed. The diagnosis was established five months before death on isolation of the fungus in cultures of biopsy tissue from the walls of the ulcer. In addition to the involvement of the tongue, the patient had histoplasmosis of the cervical and axillary lymph nodes with a possible terminal invasion of the blood stream by the parasite. He had associated Hodgkin disease of five years' duration and disseminated miliary tuberculosis, which probably caused his death. Treatment with sulfadiazine, stibamine glucoside, ("neostam") and penicillin was of no value. The mycologic, histologic and post-mortem observations are described in detail.

25. Wolff, E. K.: The Buffer Precipitation Test for Malaria (B.P.T.) Adjusted for Large Scale Examinations, Indian M. Gaz. 75:517 (Sept.) 1940.

had an opportunity to examine the section he changed his diagnosis to that of blastomycosis. The pathologist is to be excused on the ground that unless one is on guard and has an eye for the mycoses one can easily miss the observations in a section of this disorder. This fact was clearly demonstrated to me when I gave the sections for autopsy to the postgraduate students in mycology. The case was discussed at length before the sections were passed out for examination, but not one of the students was able to see the organism unaided.

Shortly after the biopsy specimen and positive cultures were obtained the patient died, and an autopsy was performed. All treatment had been without results.

I have lantern slides of all the tissues, but I will show only a few. (Slides were shown.) The first slide is a low power photomicrograph of the biopsy specimen of the skin. There is to be seen a decided inflammatory reaction with a small area of ulceration at the surface. The second slide is a high power photomicrograph of the center of this ulcerated area, showing the phagocytosed capsulated organisms in large numbers. A smear made of this ulcer would probably have made it possible to demonstrate the presence of the organisms, but this was not done. The third slide shows a section of the adrenal gland, which is commonly involved.

The next slide shows a colony of the mycelial form of the organism, which can be transformed into the yeastlike organism by various means, one of which consists of growing the organisms on sealed blood agar tubes at 37 C. The results, however, are variable and are not to be depended on. The next slide shows the yeastlike form. I have photographs of the mycelial form emerging from the yeastlike form. The last slide shows the large tuberculate spore which is necessary for the identification of the culture.

DR. MARTIN F. ENGMAN JR., St. Louis: You perhaps noticed on the map that Dr. Miller showed that St. Louis is right in the middle of the area where there have been numerous cases. Dr. Morris Moore, mycologist to the Barnard Free Skin and Cancer Hospital, has been interested in this disease and has seen about 18 patients. Reports of some of the cases have been published. His latest report of a case was published recently with Dr. Louis H. Jorstad in the *Annals of Otology, Rhinology and Laryngology*. In this report there is a fairly complete review.

This disease is of importance to dermatologists, particularly in the differential diagnosis of obscure lesions in the mouth. Of Moore's patients about a third had either mucomembranous or cutaneous lesions. In the mouth the lesions may be ulcers, plaques or granulomas of no specific type.

The disease is constitutional and spreads via the reticuloendothelial system. Regional lymph nodes become involved and may imitate Hodgkin's disease. Caseation in the lungs or the adrenal glands may occur and thus simulate tuberculosis. Sometimes histoplasmosis and tuberculosis occur together.

Dr. Miller deserves to be congratulated for his study of this disease and for bringing it to our attention. Undoubtedly we will, many of us, encounter such cases.

DR. GEORGE M. LEWIS, New York: In a patient recently observed and studied, the clinical symptoms and signs favored the diagnosis of histoplasmosis. The patient had ulcerating lesions of the tongue, splenomegaly, hepatomegaly, enlarged lymph nodes and irregular fever, with a downhill course in which the patient rapidly lost weight.

## POIKILODERMA VASCULARE ATROPHICANS

Report of a Case with Observations at Autopsy

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**A**TROPHY, telangiectasia and pigmentation, with muscular weakness, were described by Petges and Cléjat<sup>1</sup> in 1906, the same year in which Jacobi<sup>2</sup> described a complex dermatologic disease characterized by telangiectasia, pigmentation and, later, capillary hemorrhages and atrophy, which he<sup>3</sup> subsequently termed poikiloderma vasculare atrophicans. Since then over 180 cases have been presented, both as published reports and in addresses before dermatologic societies. Lane<sup>4</sup> introduced the first case to an American audience in 1920, before the New York Dermatological Society. During the last twenty-five years, approximately twenty-two papers describing this disease have appeared in the English and American literature.

In recent years the existence of poikiloderma vasculare atrophicans as a separate clinical entity has been challenged by many competent dermatologists, including Oppenheim<sup>5</sup> and Montgomery and Sullivan.<sup>6</sup>

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Read at the Sixty-Sixth Annual Meeting of the American Dermatological Association, Inc., Hot Springs, Va., June 12, 1946.

1. Petges, G., and Cléjat, C.: Sclérose atrophique de la peau et myosite généralisée, Ann. de dermat. et syph. 7:550, 1906.

2. Jacobi, E.: Fall zur Diagnose (Poikilodermia atrophicans vascularis), Verhandl. d. deutsch. dermat. Gesellsch. 9:321, 1907.

3. Jacobi, E.: Poikiloderma Atrophicans Vascularis, in Neisser, A., and Jacobi, E.: Ikonographia dermatologica, Berlin, Urban & Schwarzenberg, 1908, pt. 3, p. 95.

4. Lane, J. E.: Poikiloderma Atrophicans Vasculare, with Report of a Case by Oliver S. Ormsby, Arch. Dermat. & Syph. 4:563 (Nov.) 1921; Poikiloderma Atrophicans Vasculare: Conclusion of Previously Reported Case, ibid. 8:373 (Sept.) 1923.

5. Oppenheim, M.: Atrophien, in Jadassohn, J.: Handbuch der Haut- und Geschlechtskrankheiten, Berlin, Julius Springer, 1931, vol. 7, pt. 2, p. 500.

6. Montgomery, H., and Sullivan, R. R.: Acrodermatitis Atrophicans Chronica, Arch. Dermat. & Syph. 51:32 (Jan.) 1945.

Civatte's *poikilodermie réticulée pigmentaire du visage et du cou* was first described by him in 1923.<sup>11</sup> The characteristic feature was a reticular dark brown pigmentation, interspersed with red slightly infiltrated macules and depigmented spots, as well as superficial areas of atrophy. Civatte reported 3 cases in women during the menopause. The dermatosis started slowly, without the subjective symptoms. The first signs were seen on the forehead in the form of red infiltrations, which spread downward to the neck, shoulders, chest and arms. The main changes were on the face, but its median parts, such as the nose and the region around the mouth and eyelids, showed no changes. There was a definite border along the frontal hairline. Therapeutically, Civatte obtained improvement by using organotherapy in the form of adrenal extracts. He first stated the belief that these cases were a variety of Jacobi's *poikiloderma vasculare atrophicans*, but was finally inclined to classify them as *melanodermatitis*.

Localized patches, simulating roentgen ray dermatitis and associated with other cutaneous diseases, such as *mycosis fungoides*, have been labeled *poikiloderma vasculare atrophicans*, with resulting confusion. The following classification of *poikilodermas* will serve to emphasize the instability of the disease as a separate clinical entity: (1) *poikiloderma vasculare atrophicans* (the pure cutaneous type), (2) *poikiloderma* associated with sclerodermatous changes (*scleropoikiloderma*) and with dermatomyositis (*poikilodermatomyositis*) and (3) *poikiloderma* as the end result or sometimes the beginning of various dermatoses, for example, *acrodermatitis atrophicans chronica*, *lymphoblastoma*, *leukemia cutis*, *mycosis fungoides*, *Hodgkin's disease* and *arsphenamine dermatitis*.

#### SUMMARY OF CASES IN LITERATURE

It is difficult to summarize the literature and to generalize as to age incidence, causative factors and so forth, because all three of the types listed are described as *poikiloderma vasculare atrophicans*. It seems that this term should be limited to the pure cutaneous type and that the *poikilodermatous* changes seen in *scleroderma* and *dermatomyositis* and the similar changes seen in the lymphomas should not be called *poikilodermavascular atrophicans*. The following summary of the literature combines all three types, which are described as "PVA."

*Age.*—The ages ranged from 6 to 79 years, with an average of 33 years.

*Sex.*—There was a slightly higher incidence in women than in men.

*Occupational Hazards.*—The only common denominator among the occupational hazards was exposure to cold, mentioned specifically by

11. Civatte, A.: *Poikilodermie réticulée pigmentaire du visage et du cou*, Ann. de dermat. et syph. 4:605, 1923.

that the cutaneous picture of poikiloderma vasculare atrophicans might well be the end result of repeated insults to the skin from various factors.<sup>23</sup>

*Symptoms.*—Pruritus, slight to intense, may be present in the early stages of the disease. Cyanosis of the extremities on exposure to cold was reported in a few papers, usually in cases with associated sclerodactylia.<sup>24</sup> Arthralgia, muscle pains and weakness were noted in patients with muscular atrophy, the so-called poikilodermatomyositis.<sup>25</sup>

*Duration.*—The duration of the disease was from three months to thirty-eight years.

*Cause of Death.*—There were reports of 2 fatal cases, in which post-mortem examination gave no clue to the cause of death.<sup>26</sup> The other deaths were due to Hodgkin's disease or mycosis fungoides.<sup>27</sup>

*Physical Examination.*—The general examination revealed nothing unusual except in the patients with muscular atrophy and tenderness (poikilodermatomyositis) or with sclerodactylia and in the case described by Carleton.<sup>28</sup>

Carleton published a paper describing a case that was stated to be poikiloderma vasculare atrophicans, associated with cataracts (Rothmund's syndrome). Scleropoikiloderma has been mentioned as one

23. Oliver, E. A.: Mycosis Fungoides with Poikiloderma-Like Symptoms, Arch. Dermat. & Syph. **33**:267 (Feb.) 1936.

24. (a) Schmidt: Zentralbl. f. Haut- u. Geschlechtskr. **17**:45, 1925. (b) Rottmann, H. G.: Ueber Poikiloderma atrophicans vascularis (Jacobi) mit bemerkenswerten Nebenbefunden, Arch. f. Dermat. u. Syph. **153**:747, 1927. (c) Jaffé, K.: Zwei Fälle von Sklero-Poikilodermie, ibid. **159**:257, 1930. (d) Cross, A. G.: Case of Poikiloderma of Jacobi with Complications, Lancet **2**:1104, 1934.

25. (a) Petges and Cléjat.<sup>1</sup> (b) Oulmann.<sup>12</sup> (c) Cross.<sup>24d</sup> (d) Petges and others: Bull Soc. franç. de dermat. et syph. **36**:817 and 871, 1929. (e) Petges, G., and Petges, A.: Poikilodermatomyosite dans la jeunesse et l'enfance, Ann. de dermat. et syph. **1**:441, 1930. (f) Nicolau, M. S.: Poikilodermia avec atrophies et scleroses musculaires multiples, type Petges-Clijat (Poikilodermie myopathique), Bull. Soc. franç. de dermat. et syph. (Reunion de Strasbourg) **36**:823, 1929. (g) Ulitzka, F.: Poikilodermia atrophicans vascularis (Jakobi), Dermat. Ztschr. **54**:119, 1928. (h) Horn, R. C., Jr.: Poikilodermatomyositis: Report of a Case with Complete Postmortem Examination, Arch. Dermat. & Syph. **44**:1086 (Dec.) 1941. (i) Bruck: Dermat. Wchnschr. **68**:369, 1919. (j) Fox, H.: Poikiloderma Atrophicans Vasculare and Lymphoblastoma, Arch. Dermat. & Syph. **35**:549 (March) 1937. (k) Usher, B.: Poikiloderma Vascular Atrophicans: Report of a Case, ibid. **25**:683 (April) 1932.

26. Bowman and Clark.<sup>18b</sup> Horn.<sup>25h</sup>

27. (a) Oliver.<sup>23</sup> (b) Lane, J. E.: Poikiloderma, Arch. Dermat. & Syph. **16**:117 (July) 1927. (c) Ormsby, O. S.: Case for Diagnosis, J. Cutan. Dis. **35**:42, 1917.

28. Carleton, A.: Skin Disease and Cataract, Brit. J. Dermat. **55**:83, 1943.

of the characteristics of Werner's syndrome. However, Thannhauser<sup>29</sup> stated the belief that the cutaneous changes are different in their features in both syndromes. In Werner's syndrome the most striking feature is tightening of the skin over the underlying structures, with a paucity of subcutaneous fat tissue. Ulcers develop mainly on the points of pressure on the heels and toes, over the ankles and especially over the achilles tendon. The classification of these cutaneous diseases in the literature as "scleroderma" or "scleropoikiloderma" does not correspond to the clinical or histologic observations. In Rothmund's syndrome the cutaneous lesions are in evidence five months after birth. In contrast to Werner's syndrome, there is no stretching of the skin and no ulcers are present. Because of the recessive heredofamilial occurrence of this syndrome, it is suggested that the cutaneous changes, like the other symptoms of Werner's syndrome, are the result of a defective germ plasm, which does not manifest itself until the second or third decade of life. The designation of the cutaneous changes by a purely descriptive name, such as "heredofamilial atrophic dermatosis with cutaneous ulcers," seem more appropriate. The cutaneous changes of Rothmund's syndrome are classified in the literature as "poikiloderma" or "scleropoikiloderma." Such a classification is not in accord with the heredofamilial occurrence of the cutaneous changes nor with the histologic observations. In conformity with the designation of the cutaneous changes in Werner's syndrome, it also seems appropriate to use for these changes in Rothmund's syndrome a simple descriptive name such as "heredofamilial atrophic dermatosis with telangiectasia."

**Distribution:** The areas of distribution listed here are based on a tabulation of the literature.

Scalp. Alopecia was rare. "PVA" lesions were present in only 2 cases.

Face. In most cases the face, including the ears, eyelids (occasional transitory edema), forehead and nose, was spared.

Trunk. The lesions occurred in the back, chest, abdomen, buttocks and particularly the anterior axillary folds and in a few cases in the axillas. In 1 case there was decided distribution around the waist line, under the belt.

Extremities. The lesions were observed with equal frequency in the upper and lower extremities, with a predilection for the flexure aspects (elbow and knee). In only 1 case was the palm involved.

Mucous membrane. There were two or three reports of leukoplakia, "white reticulation," on the inner aspect of the cheek.

**Symmetry:** The distribution was symmetric in all but 1 case.

29. Thannhauser, S. J.: Werner's and Rothmund's Syndrome, Ann. Int. Med. 23:559, 1945.

**Evolution:** Gougerot<sup>30</sup> stressed the early lichenoid papule or red patch, the size of a millet seed, as the primary lesion and stated that the disease was slowly progressive. In 1 case the patches were present for eighteen years. No other authors mentioned the evolution of the lesion.

**Description:** The lesions<sup>31</sup> presented a variegated pattern, consisting of an admixture of telangiectasia, atrophy, hyperpigmentation, depigmentation, miliary lichenoid papules and capillary hemorrhages, the whole being covered with fine furfuraceous scales. The color varied from pale pink through dark brown to livid or rose red, depending on the number of areas of telangiectasia. As the areas were set more closely together, the color became deeper. Characteristically, there were islands of atrophic spots, surrounded by a hyperemic pigmented network, by dark pigmentation and partly by bright red to livid marbling, with numerous areas of telangiectasia and capillary hemorrhages. The hair follicles appeared as darkly limited red brown spots, the size of a pin-head. Ulcers or scars of ulcers were seen.

**Laboratory Examination.**—Studies of the chemical composition of the blood revealed the nonprotein nitrogen to be normal. The total protein was elevated in 1 case. There was a low level of vitamin C. Creatinuria was observed in cases with involvement of the muscles. Hematologic studies revealed nothing abnormal. Wassermann reactions were negative, and the urine was normal. Roentgenologic examination revealed subcutaneous calcification in several cases.

#### REPORT OF A CASE

A 67 year old retired construction worker, of Lithuanian extraction, was admitted to the Boston City Hospital on Jan. 18, 1944, with the chief complaint of progressive scaling and itching, of six months' duration.

The patient had been in good health until six years previous to admission, when cellulitis developed following a cut on the finger. In July 1943, after repeated swims in salt water and prolonged sun baths, the patient noticed an

30. Gougerot, H., and Eliascheff, O.: La petite papule rouge, lesion élémentaire et initial de la poikilodermia reticuleuse de Petges-Jacobi, Arch. dermat.-syph. de la clin. de l'Hôp. Saint-Louis **1**:137, 1929.

31. (a) Dowling, G. B., and Freudenthal, W.: Dermatomyositis and Poikilodermia Atrophicans Vasculare: A Clinical and Histological Comparison, Brit. J. Dermat. **50**:519, 1939. (b) Taussig, L.: Poikiloderma Atrophicans Vasculare, Jacobi: Report of a Case with a Review of Recent Literature, Arch. Dermat. & Syph. **25**:882 (May) 1932. (c) Parounagian, M. B.: Poikiloderma Atrophicans Vasculare, ibid. **29**:915 (June) 1934. (d) Hazel, O. G.: Poikiloderma Atrophicans Vasculare: Report of a Case, ibid. **40**:776 (Nov.) 1939. (e) Bechet, P. E.: Poikiloderma Atrophicans Vasculare, ibid. **29**:462 (March) 1934. (f) Perlstein, M. O.: Poikiloderma Atrophicans Vasculare, ibid. **29**:158 (Jan.) 1934. (g) Photinos, P. B.: Contributions to the Clinical Symptoms and Histology of Poikilodermia of Petges-Jacobi, Dermat. Wchnschr. **93**:1461, 1931. (h) Counter, C. E.: Poikiloderma Atrophicans Vasculare, Arch. Dermat. & Syph. **49**:85 (Jan.) 1944.

area of bluish discoloration, approximately 3.5 cm. in diameter, on the dorsal aspect of his right wrist. The skin in this area appeared to be coarser than the surrounding skin and was covered by fine silvery branlike scales, associated with itching and a papular eruption. By the following month the lesion had spread by continuity to involve the entire right arm and hand, with the exception of the palm and the elbow. The itching became severer and was worse at night. There were no symptoms associated with any other systems. During this period and throughout September the patient took sun baths in the nude for six to eight hours daily. He noticed no change in pigmentation in the affected areas other than tanning. The eruption spread to involve the neck, back, lower extremities, abdomen, chest and left arm and lastly the scalp and face. The elbows, palmar and plantar surfaces, and genitals were spared. The right upper eyelid was also involved.

Between October 1943 and January 1944, the skin became dry, atrophic and finely pleated, presenting a cigaret paper appearance. Two weeks before admission there was painless bleeding from the lesions, due partly to scratching and partly to fissuring.

The family and occupational histories were noncontributory. There were no other subjective symptoms besides those of the skin. The appetite was excellent, and the diet was adequate.

Physical examination revealed a robust, well developed, and well nourished man, in no apparent distress; except for the skin there were essentially no abnormalities. The entire cutaneous surface had such a peculiar color that the patient's race was undeterminable at first glance. The outstanding features were the reticulated appearance, the pleating, most evident at the flexural folds, and the dry adherent furfuraceous scaling of the entire surface, with pinhead-sized ecchymoses and brilliant red patches. The skin was freely movable throughout and showed no evidence of sclerosis. The color varied from a light yellowish white to a dark dirty brown. The light areas were atrophic and tended to be circular, smooth and surrounded by a dark reddish or purple border; some were confluent and others discrete. The scalp was bald at the vertex and surrounded by light atrophic parietal and occipital areas. The skin of the scalp was covered with deeply pigmented circular patches, 1 to 1.5 cm. in diameter and surrounded by light atrophic areas. The forehead and cheeks, especially in the malar area, were deeply pigmented and almost blackish brown. The eyelids, especially the right one, were edematous and deeply pigmented. The ears were atrophic and reddish pink, especially the upper half; the lower part was pigmented. The body and extremities were fairly well developed, with fairly firm musculature. The nipples were heavily pigmented, and the skin showed varying degrees of pigmentation, with scattered atrophic areas similar to those on the scalp. Over the left clavicle and midsternum there were brilliant red areas, with fine punctate ecchymoses and scattered areas of telangiectasia. Similar areas were present on the inner aspect of the arms. Most of the hair was absent from the follicles, which frequently showed minute hemorrhages. On the posterior aspects of the arms and the chest there were areas of what appeared to be typical roentgen ray dermatitis, brilliant erythema, dryness and thin loosely adherent scaling, with alternating areas of decided pleating, pigmentation and telangiectasia. On the arms were areas of decided pleating, scaling and anetodermia of varying degrees of pigmentation, and capillary hemorrhages. The genitals presented a few lichenoid papules, with crinkling, atrophy and furfuraceous scaling. The appearance of the legs was similar to that of the arms, but the areas of depigmentation were surrounded by red violaceous borders.

The feet were slightly edematous and pigmented, with furrowing of the anterior aspect of the ankles. The veins were not prominent. The infra-red film showed no enlargement of the vessels. There were occasional excoriations on the body and extremities. There were no vesicles or bullae, and none were ever present throughout the patient's illness.

The white cell count was 7,000, with 6 per cent young forms, 46 per cent mature forms, 38 per cent lymphocytes, 6 per cent monocytes, 3 per cent eosinophils and 1 per cent basophils. The nonprotein nitrogen in the plasma was 38 mg. per hundred cubic centimeters, the serum calcium 10.3 mg., the serum phosphorus 4

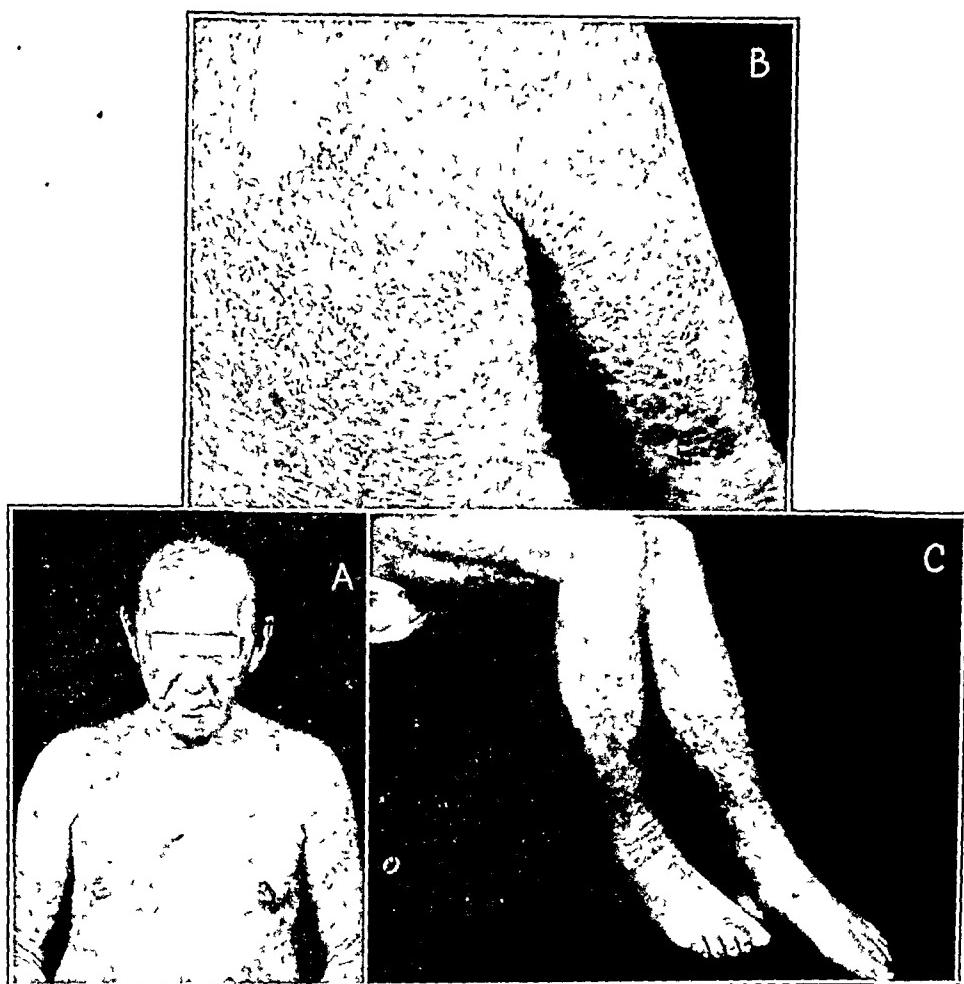


Fig. 1.—*A*, generalized pleating and scaling, with telangiectasia and circular areas of atrophy surrounded by reticulated pigmentation. The dark areas were brilliant red because of capillary dilatation and hemorrhages. *B*, posterior aspect of the chest and arm showing a peculiar clam shell scaling, with atrophy and telangiectasia resembling a roentgen ray burn, and decided pleating. *C*, reddish violaceous lacework pattern on the legs, due to dilated capillaries and increased pigmentation, and scaling on the dorsa of the feet, with pleating at the anterior aspect of the ankles.

mg. and the serum phosphatase 4.3 Bodansky units. The corrected sedimentation rate was 19 mm., 16 mm. and 13 mm. per hour. The hematocrit reading was 41.5 per cent, the icteric index 5 units and the prothrombin time 100 per cent. The

Gross Observations: The body was that of a well developed cachectic-appearing white man of about 65 years. There was an offensive odor to the body, and practically the entire skin was involved in an abnormal process. The skin of the right thigh was thin and parchment-like and had scattered purple-red areas. On the legs there were scaling and dryness of the skin. On the left foot, mesially and anteriorly, there was loss of epidermis and subcutaneous tissue, the result of a recent burn. The chest, back and abdomen revealed loss of the surface layers of the skin, with a moist layer visible. There were numerous foci that were infected and foul smelling, and the skin in many places was covered with so-called triple dye.

The pupils were equal in diameter, and the hair of the scalp was sparse. There was no jaundice or pitting edema of the lower extremities.

The peritoneal cavity contained old adhesions, which coursed from the omentum to the anterior parietal peritoneum. The appendix appeared normal. The stomach and small intestine were moderately distended. The edge of the liver was 2 cm. below the right costal margin. The right pleural space contained old adhesions, laterally and posteriorly. The left pleural space was normal.

The pericardial cavity contained 15 to 20 cc. of straw-colored fluid; there were no adhesions. The heart weighed 375 Gm. The left ventricle was dilated, and the myocardium was unusually flabby and brown-yellow. Otherwise, the heart was essentially normal. The right lung weighed 860 Gm. and the left lung 740 Gm. The bronchi were injected, and the right main bronchus contained friable material, apparently aspirated. The cut surface of the lungs revealed dark red unusually moist parenchyma, with no areas of consolidation. The spleen weighed 400 Gm., and the capsule was smooth. The cut surface was pink-red and soft, and the follicles were indistinct. The liver weighed 2,100 Gm., and the capsule was smooth. The cut surface was pale brown, with indistinct vascular markings. The kidneys weighed 340 Gm. The capsules stripped with some difficulty from smooth surfaces. The cut surface was red-brown, with a well demarcated cortex. The pelvis and ureters appeared normal. The aorta was smooth and elastic, with minimal arteriosclerotic involvement. The remainder of the gross autopsy observations, essentially, were not unusual.

Bacteriologic Study: The right lung contained *Clostridium welchii*, *Escherichia coli* and *Proteus vulgaris* and the left lung *C. welchii* and *P. vulgaris*.

Microscopic Study: Sections were fixed in Zenker's fluid and stained with phloxine-methylene blue.

Heart: The myocardium showed localized collections of interstitial leukocytes, with a few polymorphonuclear cells and in places numerous lymphocytes. The muscle bundles showed no change.

Lungs: In the pulmonary vessels there was rather decided thickening of the walls. The alveolar spaces contained amorphous granular material. Numerous large mononuclear cells were noted at times, adjacent to plump rod-shaped organisms. In numerous alveolar spaces there were mononuclear cells, granular debris, with occasional black granular material, and shadows of what appeared to be red blood cells.

Liver: There were focal accumulations of lymphocytes, with fibrosis in one small area close to such a collection of cells.

Kidney: The capsule was slightly thickened, and there were numerous focal collections of lymphocytes replacing glomeruli and tubules. In places there was fibrosis of the parenchyma, with scattered lymphocytes nearby, as well as dilated tubules containing amorphous purple-staining casts. The interstitial tissue was

infiltrated in an irregular fashion, with small collections of lymphocytes. The tubules appeared widely separated by a collection of amorphous material, which seemed to separate the fibrillar strands of the interstitium. The glomeruli showed varying degrees of increase in the thickness of basement membranes, with minimal pericapsular fibrosis. The arterioles presented moderate reduction in the width of the lumens.

The microscopic sections of the other organs were essentially normal.

Skin (right thigh): The epidermis appeared thinned, particularly the prickle cell layer; the intercytoplasmic processes stood out prominently. The epidermis appeared flattened, and the rete cones were not prominent. Beneath the stratum

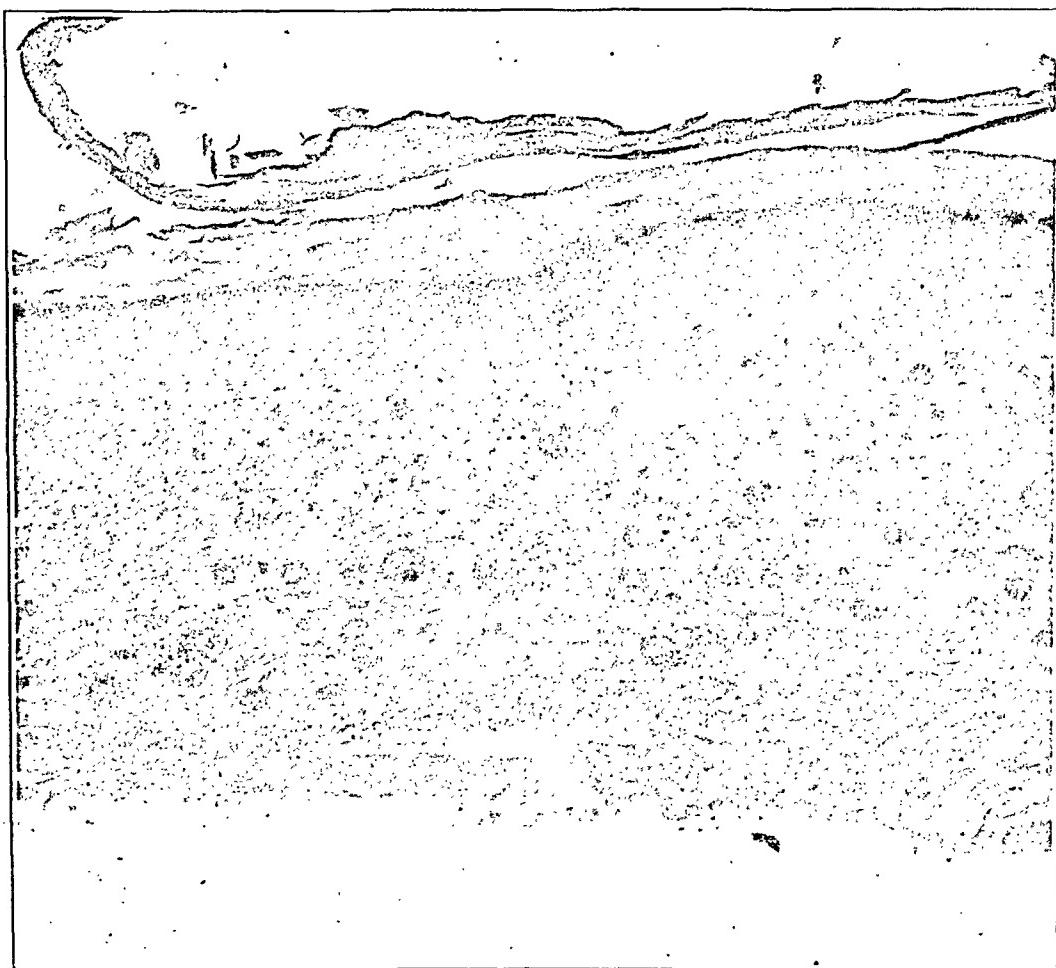


Fig. 3.—Section of skin from the abdomen, showing hyperkeratosis, loss of prominence of rete pegs, inflammatory infiltrate and numerous distended and thickened blood vessels.  $\times 80$ .

germinativum were numerous foci of lymphocytes infiltrating the pars papillaris of the cutis and prominent capillaries, which were distended. Granules of yellow-brown pigment stood out in cells of the papillaris area of the cutis (fig. 3 and 4).

Abdomen: The outstanding changes were the presence of dense foci of lymphocytes, with an occasional plasma cell in the pars papillaris, immediately below the epidermis. There was no border zone of connective tissue separating the inflammatory infiltrate from the epidermis. The cutaneous appendages, such as sweat glands and hair follicles, showed no significant changes. The epidermis was

somewhat thinned, and the rete cones were not prominent. In the large vessels there was moderate to advanced thickening of the walls, apparently mainly a thickening of the medium.

Elsewhere in the section there were numerous polymorphonuclear leukocytes infiltrating the pars reticularis and extending into the pars papillaris. Many lymphocytes were also present in the pars reticularis.

**Special stains.** Sections were fixed in Zenker's fluid and stained for iron by Gomori's method and for elastic tissue by the Verhoeff method. Sections from

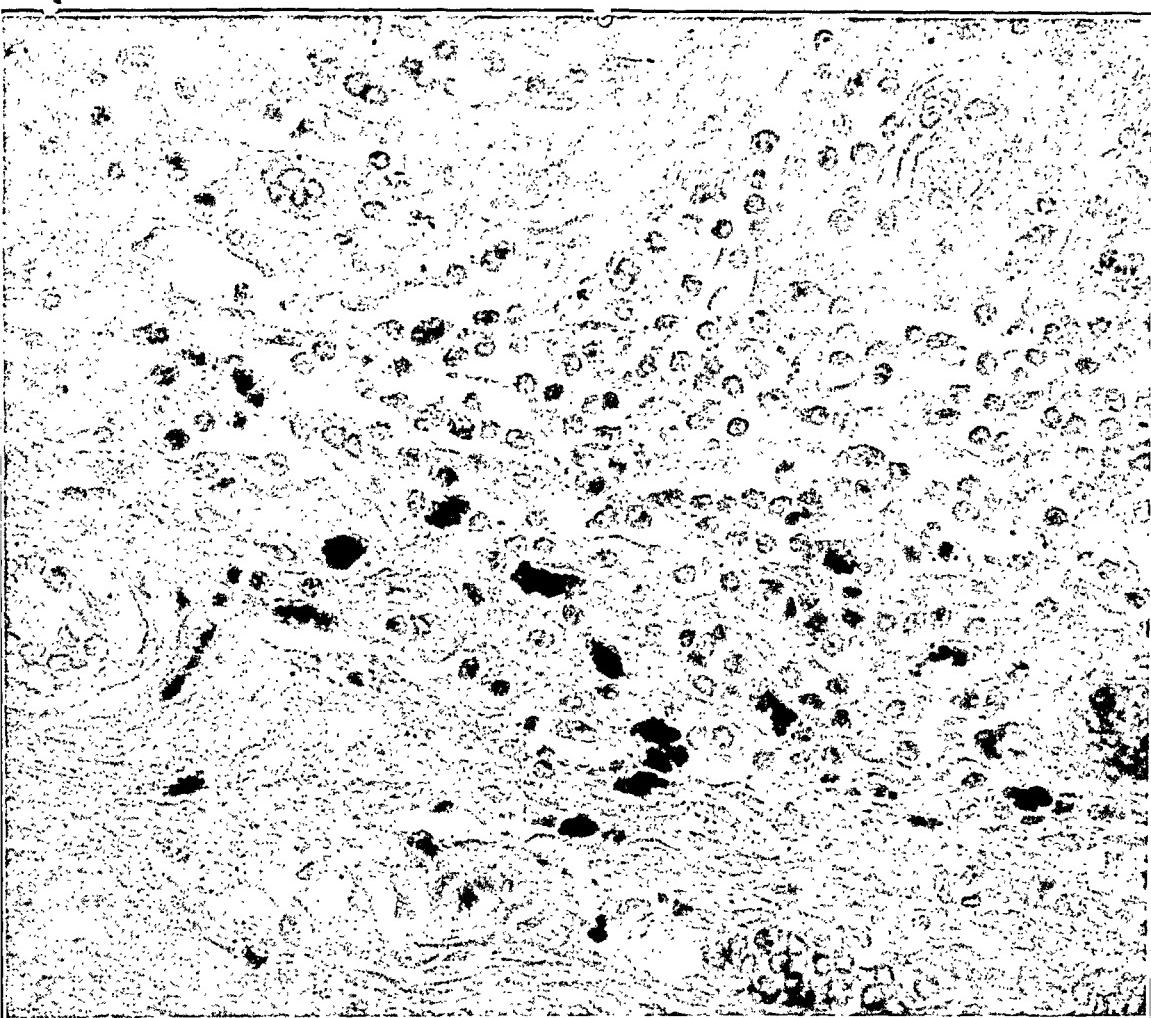


Fig. 4.—Section of skin from the right thigh, showing inflammatory infiltrate, chromatophores and prominent blood vessels.  $\times 650$ .

the thigh and abdomen stained for iron failed to reveal the presence of iron pigment in the chromatophores, situated mainly in the pars papillaris of the cutis. Sections from the same sites stained for elastic tissue revealed almost complete loss of the tunica elastica in the cutis where the inflammatory infiltrate was noted.

**Striated muscle.** There were no significant changes. In the smaller blood vessels there were minimal thickening of the walls. No inflammatory infiltrate of cells was noted.

studies of the blood revealed no evidence of infiltration of the skin or blood dyscrasias and no evidence of Hodgkin's disease, the terminal ending in Lane's famous case.<sup>27b</sup> Lymphosarcoma, the terminal disease of Ormsby's patient,<sup>27c</sup> should have been revealed at autopsy. There was no evidence of sclerosis or of myositis, as described by Petges and Cléjat.<sup>1</sup> At no time did this patient receive roentgen ray therapy. He never showed any sign of sclerosis, and the veins were not prominent, which rules out the possibility of association with scleroderma or acrodermatitis chronica atrophicans.

If one keeps in mind the picture of a patient suffering from an intense itch, but no other subjective symptoms, with scaly pleated skin, showing atrophic patches surrounded by reddish pigmented network, shining punctate hemorrhages and telangiectasia, there should be no difficulty in classifying this case as one of poikiloderma vasculare atrophicans, especially since the histologic picture presents the characteristics herein described.

#### HISTOLOGIC STUDIES

Poikiloderma vasculare atrophicans of Jacobi, listed under the diseases with cutaneous atrophy,<sup>32</sup> is characterized by widespread telangiectasia, pigmentation and cutaneous atrophy. This report presents a case that at autopsy had been diagnosed clinically as poikiloderma vasculare atrophicans. The following histologic changes were evident: thinning and flattening of the epidermis, loss of prominence of the rete pegs, increased deposition of pigment in chromatophores in the region immediately beneath the flattened epidermis (iron stains showed this pigment not to be iron), subpapillary lymphocytic foci and vascular dilatation and prominence in the pars papillaris of the cutis. Further studies revealed decided loss of elastic tissue in the region of the cutis, where the inflammatory infiltrate was most dense. The striated muscle showed no changes, and the fat appeared normal. However, it appeared that the muscle bundles were spread apart by amorphous pink-staining material (edema of the tissues). It is believed that the histologic features of this case are consistent with the clinical diagnosis of poikiloderma vasculare atrophicans, and the histologic changes in the skin are similar to those described in other papers.

In addition to this case, we were recently permitted to review some of the microscopic sections of Montgomery and Sullivan and the histologic protocols and microscopic sections of Weidman,<sup>8</sup> as well as slides from the Army Medical Museum.

In Lane's<sup>4</sup> résumé of the nature of this disease, he stated that two stages are noted. In the first stage, there are perivascular infiltration of round cells and dilatation of the superficial vessels, with alternate increase and diminution or absence of pigment. In the second stage,

32. Ormsby, O. S.: Diseases of the Skin, ed. 5, Philadelphia, Lea & Febiger, 1937, p. 586.

the papillae are flattened and there are degeneration and disappearance of the elastin and atrophy of the collagen bundles. Early cases of poikiloderma vasculare atrophicans may show sharply localized areas of atrophy and condensation of the epidermis. In the corium the only pathologic change consists of a slight perivascular round cell infiltration at the level of the subpapillary plexus of vessels. The cells are mostly lymphocytes. Such changes are unassociated with edema, either in the corium or in the papillae. Other reports have emphasized the atrophy of the epidermis, the destruction of the basement membrane as a result of the extension of the round cell infiltrate from the corium well into the epidermis, severe edema of the papillary and subpapillary areas, hyperplasia of arterioles and cellular infiltrate in the corium; diffuse in distribution.

Diseases that have frequently been considered in the differential diagnosis are acrodermatitis chronica atrophicans, disseminated lupus erythematosus, dermatomyositis and scleroderma. It is thought that the histologic features of the case herein reported differ from those about to be presented and that therefore poikiloderma vasculare atrophicans can be differentiated from other cutaneous diseases with which it is often confused.

Montgomery and Sullivan<sup>6</sup> expressed the belief that the histologic changes in acrodermatitis chronica atrophicans are diagnostic in practically all cases if a specimen for biopsy is taken from a well developed region, independent of any associated fibrous nodules, sclerodermatous changes or ulcers. The following combination of changes makes a diagnostic picture: relative to absolute hyperkeratosis, preservation of a granular layer, atrophy and flattening of the prickle cell layer, loss of rete ridges and papillary bodies, with resultant flattening of the epidermis into a thin wavy line, and a definite grenz or border zone of normal to homogenized connective tissue between the epidermis and the infiltrate in the cutis. Much emphasis is laid by the authors on this zone, which is apparently characteristic of acrodermatitis chronica atrophicans and is not seen in poikiloderma or other diseases. Also, in poikiloderma liquefaction degeneration of the basal cell layer occurs, a change that is not seen in acrodermatitis. Another possible differential point is the presence of chromatophores in poikiloderma, containing a non-iron pigment in the pars papillaris of the cutis, whereas these are not observed in acrodermatitis. Some of the more unusual features of acrodermatitis chronica atrophicans, such as fibrous nodules, arthritis deformans, ulnar bands, scleroderma-like changes and involvement of the mucous membranes, may permit ready differentiation from poikiloderma and other cutaneous diseases.<sup>33</sup>

33. Sweitzer, S. E., and Laymon, C. W.: Acrodermatitis Chronica Atrophicans, Arch. Dermat. & Syph. 31:196 (Feb.) 1935.

In contrast to poikiloderma and acrodermatitis, the pathologic changes of disseminated lupus erythematosus are frequently distinctive, so that these entities may be separated. However, Montgomery<sup>34</sup> stated that the histologic picture of poikiloderma vasculare atrophicans of Jacobi may simulate the telangiectatic or atrophic changes of disseminated lupus erythematosus. Characteristic pathologic changes in the latter disease consist of relative and absolute hyperkeratosis, keratotic plugging of hair follicles and sweat ducts, preservation or even thickening of the granular layer, acanthosis of the prickle cell layer with adjacent regions of atrophy, liquefaction necrosis of the basal cell layer, dilatation of the superficial capillaries and lymphatics, edematous changes in the cutis and destruction of elastic tissue where the infiltration occurs and the presence of a varying number of chromatophores laden with melanin. In all types of lupus erythematosus, according to Montgomery, there is slight but definite increase in the number of lattice fibers, which to him suggested involvement of the reticuloendothelial system.

Klempener,<sup>35</sup> on the other hand, emphasized the degenerative phenomena in disseminated lupus erythematosus and pointed out that infiltration of inflammatory cells is scant. The earliest change, according to him, is shown as homogenization of the collagen fibrils and ground substance in the most superficial layer of the corium. The ground substance and fibers undergo fibrinoid degeneration as the process advances. The vascular lesion in the skin is evidently determined by involvement of the connective tissue matrix of the corium, which is continuous with the connective tissue of the vessel wall. The degenerative changes in the epidermis are considered secondary to changes in the connective tissue of the corium and its blood vessels. The vascular changes, according to the same author, show as a deposit of homogeneous eosinophilic material within the tunica intima, between muscle fibers, or in the tunica adventitia. A further change is the deposition of rings of fibrinoid material in the tunica intima, choking the lumen. With complete fibrinoid change of the collagenous framework of the vessel wall, destruction of muscular and elastic elements takes place. These changes, described in the blood vessels and in the ground substance of the corium, are not seen in poikiloderma or acrodermatitis.

Dermatomyositis and scleroderma are so commonly confused that these diseases are considered separately and also are compared as to their histologic features. In a case of fatal acute diffuse scleroderma reported by MacCallum,<sup>36</sup> microscopic studies revealed no changes in

34. Montgomery, H.: Pathology of Lupus Erythematosus, *J. Invest. Dermat.* **2**:343, 1939.

35. Klempener, P.; Pollack, A. D., and Baehr, G.: Pathology of Disseminated Lupus Erythematosus, *Arch. Path.* **32**:569 (Oct.) 1941.

36. MacCallum, W. G.: Acute Diffuse Scleroderma, *Tr. A. Am. Physicians* **41**:190, 1926.

not significant. The authors stated that the lesions of the muscles in dermatomyositis appear to be of sufficient diagnostic import to warrant the separate classification of the two diseases. In many places the muscle fibers had an amorphous appearance, with loss of the usual fibrillar structure. In these areas striations were lost, the fibers had large and small vacuoles, or there was a loss of the sarcolemma nuclei. These changes occurred singly or in combination. There was widespread edema, not only between the muscle bundles but between the individual muscle fibers as well. There were patches of exudate throughout the muscle bundles, composed of small lymphocytes, plasma cells and a rare polymorphonuclear leukocyte. Some of the muscle fibers had been replaced by pale-staining fibrous connective tissue. There was a decided perivascular infiltrate by an exudate similar in character to that seen in the muscle.

Brock,<sup>40</sup> comparing the histologic features of scleroderma and dermatomyositis, pointed out that the inflammatory infiltrate in the former is minimal, whereas the same process in dermatomyositis is a cardinal feature. The parenchymatous degeneration of muscle is varied and diffuse and constitutes a cardinal feature of dermatomyositis, whereas in scleroderma this change is not prominent and is usually proportionate to the interstitial sclerosis. The vascular changes, according to this author, are minimal in dermatomyositis and a cardinal feature in scleroderma. He concluded by stating that the connective tissue changes and sclerosis of scleroderma are distinctive and form another link in the attempt to differentiate the two entities.

#### CONCLUSIONS

A case is reported, with observations at autopsy, of a man with a cutaneous disturbance consisting of reticulated atrophy, telangiectasia and pigmentation, similar to that termed by Jacobi as poikiloderma vasculare atrophicans. Death resulted from hemorrhage and toxemia of the skin. Autopsy revealed the disease of the skin to be the primary cause of death.

The following histologic changes are distinctive of poikiloderma vasculare atrophicans: thinning and flattening of the epidermis, loss of prominence of the rete pegs, increased deposition of pigment in chromatophores in the region immediately beneath the flattened epidermis (iron stains revealed this pigment not to be iron), subpapillary lymphocytic foci and vascular dilatation and prominence in the pars papillaris of the cutis.

Physical factors, such as exposure to extremes of temperature and actinic radiation, should be considered as precipitating factors in the

40. Brock, W. G.: Dermatomyositis and Diffuse Scleroderma: Differential Diagnosis and Reports of Cases, Arch. Dermat. & Syph. 30:227 (Aug.) 1934.

onset of this disease. In the present case, the sole causative factor appeared to be overexposure to sunlight. Although localized patches of the dermatologic complex called poikiloderma may occur in other diseases, there is a generalized disease called poikiloderma vasculare atrophicans that is a distinct clinical and histologic entity.

This case proves that not in all patients showing the clinical picture of poikiloderma vasculare atrophicans do symptoms of another disease, such as mycosis fungoides, develop. It emphasizes the importance of recognizing individual clinical entities for the purposes of treatment and prognosis. The mere fact that in some patients presenting poikiloderma or psoriatic lesions a picture of mycosis fungoides later develops does not mean that there is no disease entity that should be labeled poikiloderma vasculare atrophicans or psoriasis.<sup>41</sup>

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#### ABSTRACT OF DISCUSSION

DR. STUART C. WAY, San Francisco: I am indebted to Dr. Downing for this opportunity to discuss his interesting and excellent paper. His photographs, too, were fine. From every standpoint, the case appears to represent a typical example of poikiloderma atrophicans vasculare and is, judging from the photographs, one with the most extensive involvement that I have seen.

While Dr. Downing's clinical and microscopic studies tend to establish poikiloderma atrophicans vasculare as an entity, reports of cases by other men present much to be overcome. Regardless of the fact that antemortem and postmortem observations in this case were insufficient to establish the cutaneous changes as secondary to Hodgkin's disease, lymphosarcoma, mycosis fungoides and neurosyphilis, the presence of the changes during the terminal phase of other reported cases cannot be overlooked, as has been brought out by Foerster, Hazel, Jacob and others. Although the dermal pathologic changes did not appear to be secondary to or associated with a primary cause, such a possibility did exist, however undiscoverable it may have been.

I do not recall whether the brain tissues were examined at the time of the autopsy. This is a necessary procedure, however, as there is reason to believe that dermal pathologic changes may be due to degenerative changes of the central nervous system.

Until several days ago it was my impression that the various reported cases, especially the recent case of Kalz and Hoogstraten, had practically stabilized the status of poikiloderma atrophicans vasculare as a cutaneous symptom of a number of known and unknown diseases and had removed it from the clinical entities.

These authors described a case of the Jacobi type, associated with meningo-vascular neurosyphilis, in which the cutaneous manifestations completely responded to bismuth compound, arsenic and hyperpyrexia therapy.

It is difficult to evaluate the part played by the fever therapy, although I have observed that scleroderma, a disease in some respects not unlike poikiloderma atrophicans vasculare, occasionally shows some response to localized heat, especially infra-red.

41. Dr. F. Parker Jr. contributed to the preparation of this paper.

Past reports of cases emphasize the necessity for examining patients with poikiloderma atrophicans vasculare from a neurologic, endocrinologic, hematologic and vascular standpoint.

DR. HAMILTON MONTGOMERY, Rochester, Minn.: I enjoyed Dr. Downing's paper. I have been working with Dr. Helen J. Hare on a group of some 20 cases of poikiloderma, possibly 3 of which would be regarded as of the idiopathic type. Jacobi's original case was that of a farmer who had atrophy of the shoulder muscles and drooping of the head, which suggest strongly that his case was one of poikilodermatomyositis. Petges reported cases of poikilodermatomyositis, but he still differentiated Jacobi's case from his own. Oppenheim in his discussion of Cannon's paper expressed the thought that Petges' cases and Jacobi's case were similar.

Dr. O'Leary and other members of our department have seen a number of cases of dermatomyositis with poikiloderma-like changes. The cases of poikiloderma vasculare atrophicans which have been reported in this country by Lane, Ormsby, Oliver and others have been cases that have eventuated in mycosis fungoides or lymphoblastoma. I have seen 7 such cases. Dr. Ormsby and Dr. Otto Foerster were hesitant to accept as poikiloderma of Jacobi a case that I presented with Dr. O'Leary in 1932, at a meeting of the Chicago Dermatological Society, because the man in this case showed some changes suggesting a pituitary disturbance. That man was seen later by Dr. Osborne, at which time mycosis fungoides had developed. He died about ten years later of lymphosarcoma.

Extensive poikiloderma may also be seen in patients with endocrine disturbances, as illustrated by the disease in a child whom I saw recently with so-called Rothmund syndrome. (A slide was shown.) There was deformity of the bones of the hand, but no evidence of dermatomyositis. The disease started at 3 years of age. I have seen several cases of poikiloderma as an end stage of subacute disseminate lupus erythematosus. I had 1 case of localized traumatic poikiloderma, similar to the second case that Dr. Downing reported.

I reported with Dr. R. R. Sullivan a case of extensive poikiloderma in association with acrodermatitis chronica atrophicans in a patient who had previously been presented by Dr. Graham before the New York Dermatological Society (ARCH. DERMAT. & SYPH. 51:32-46 [Jan.] 1945). In other words, poikiloderma vasculare atrophicans may represent a syndrome and not a disease entity. On the other hand, just before coming to the meeting, I saw a man aged 73 who had a classic picture of poikiloderma and who gave a history of having had the disease for forty years, without progression and without ever having had treatment of any sort. His general examination did not reveal any abnormalities. There were 2 other cases in which the disease was of shorter duration and in which we were unable to demonstrate any other cutaneous or systemic disease.

DR. WILLIAM H. GOECKERMAN, Los Angeles: I have been particularly interested in Jacobi's poikiloderma vasculare atrophicans since 1920. At that time I saw in an old edition of "Ikonographia dermatologia" what I thought was a classic case, and since then I have been particularly interested. I can say offhand that while one sees many poikiloderma-like changes, one seldom sees a typical picture. At least, to my eye they are not typical; they are not even strongly suggestive.

It is often stated that this type of poikiloderma resembles radiodermatitis or actinic dermatitis. I cannot see the close resemblance except in exceptional cases. Only occasionally does one see old radiodermatitis which at all resembles poikiloderma of Jacobi. These poikiloderma-like changes, of course, are seen in some patients with Riehl's melanosis and some types of lupus erythematosus disseminatus, and are occasionally seen in lymphoblastoma and such diseases, but I cannot see that they closely resemble the true Jacobi type of poikiloderma.

Montgomery's note on his recent case of thirty years' duration, while I did not see the patient, suggested to me the possibility of a typical case of the Jacobi type. Since I have followed this cutaneous picture with much interest, I discussed the situation with Gans repeatedly, but he was rather noncommittal. In 1930 I had the chance to visit with Professor Jadassohn for some time, and naturally we discussed many borderline problems, including poikiloderma. He had seen the originally reported case and readily said that it had nothing to do with lupus erythematosus, although when it was first presented he had favored that diagnosis. He also readily admitted that it was a typical picture, and as we went along he said, "I will show you," and he showed me a typical picture.

I cannot see that this picture in any way resembles that with the common poikiloderma-like changes, if a critical attitude is taken, and I think that for the purposes of scientific study we should be more critical of the picture as seen in the skin. I have seen only 2 patients with the disease, plus 1 in Europe, and I lean to the opinion that these patients have a congenital anomaly of some type in which the cutaneous manifestations are probably brought out, as in Dr. Downing's patient, by some irritation. Without that, the anomaly might not be manifest for many years.

Maybe it would be better if it were called a biologic inferiority rather than a congenital anomaly, but I do not believe that this picture, if it is followed critically, is distinct. Rothmund's syndrome on the skin does not in any way suggest it. Because of the diagnostic acumen of Dr. Paul Anderson, I saw a typical case in Los Angeles, but the picture of poikiloderma of Jacobi, to me, was not suggested for a moment.

I was glad to hear Dr. Downing take the point of view that he did, but I would like to feel that one should be more critical in interpreting the morphologic picture as is seen on the skin. It must be rare, because I have followed it in the meetings and elsewhere with much interest and have seen only 2 cases that I would place in that category from a purely morphologic standpoint.

DR. FREDERICK R. SCHMIDT, Chicago: I enjoyed Dr. Downing's presentation, particularly his statement that we have been disappointed in our observations at autopsy in cases of cutaneous disease. I think that one should look to living tissue for the explanation of some of these changes in the skin. A man who has a coronary disease and who has had an attack and has survived is warned by his physician to avoid three things particularly: emotion, exertion and cold. Why? Because these three things release epinephrine. Epinephrine works as a vasoconstrictor on the coronary vessels and produces the anoxia which is the cause of the cardiac failure.

This pertains to the physiology of the skin in the same way. When cold is applied to the skin, there is an immediate response and histamine is produced with vasoconstriction and subsequent vasodilatation. This vascular reaction is irreversible. It cannot be reversed and still leave a normal blood vessel.

The same thing pertains to lupus erythematosus with respect to sunlight. After exposure to sunlight, there is damage done to the blood vessels, which process is again irreversible. Not only is histamine produced, but there are certain vitamins in the skin, water-soluble vitamins, such as riboflavin, which are destroyed by sunlight, and that process cannot be reversed. Therefore, I heartily subscribe to the premise in Dr. Downing's interesting paper that external factors, such as cold, play a role in the case of housewives and other persons who are repeatedly exposed to cold, whose skin may be damaged irreparably, as in the case after exposure to sunlight.

DR. JOHN GODWIN DOWNING, Boston: I wish to thank all the discussers. In answer to Dr. Way, I wish to say that this man never showed any signs of syphilis: His history and clinical and laboratory examinations revealed no abnormalities. I visited this man frequently in order to keep him contented at the hospital—he was an interesting and intelligent conversationalist. Unfortunately, my colleagues and I were unable to get permission to examine the brain.

In order to emphasize another physical factor in the precipitation of this disease, I would like to show three slides illustrating successive stages of another case of poikiloderma vasculare atrophicans. They picture a 48 year old man who was an iceman for twenty-eight years. He usually carried the ice on his left shoulder. In the process of loading it, he placed the load on the anterior aspect of the upper third of either thigh and on the iliac crest and then lifted it to the shoulder, usually the left. These slides show colored photographs of areas of poikiloderma, corresponding to the sites of greatest contact with the ice. I plan to publish a report of this case later.

## SIMPLE PLASTIC MOUNT FOR PERMANENT PRESERVATION OF FUNGI AND SMALL ARTHROPODS

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WE HAVE employed with success, as a medium for the mounting and clearing of biologic specimens, a recently synthesized resin, or plastic, polyvinyl alcohol, known commercially as "PVA."<sup>1</sup> This substance when combined with lactic acid and phenol provides a permanent hyaline mount and also clears and dehydrates the specimen in a satisfactory manner. The latter features are especially advantageous when it is desired to preserve for teaching purposes or for study collections such biologic forms as the scabies mite, ticks, fleas and lice or their ova. In the preservation of cutaneous fungi, the method is adaptable to material removed from ordinary cultures of fungi, actively growing slide cultures and material in the form of scrapings of skin for the purpose of direct microscopic study.

Polyvinyl alcohol was first employed in biologic work by Lubkin and Carsten<sup>2</sup> as a medium for the elimination of dehydration in the preparation of tissues by histologic technic. More recently Downs<sup>3</sup> reported in detail on its use in the preservation of mosquitoes and their larvae, Giemsa-stained blood films, trematode cercariae, motile micro-organisms and pollen grains.

Polyvinyl alcohol is a white powder, or amorphous granular substance, which is soluble or dispersible in water. The aqueous solution is clear and syrupy in consistency, and the viscosity of the solution may be varied by the amount of water added. Films prepared from this substance are resistant to ether, xylol and acetone. We have prepared

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1. "PVA" (Grade RH-349), a synthetic polymer of vinyl alcohol, is available through the E. I. du Pont de Nemours Company, R. & H. Chemical Department, Niagara Falls, New York, at a cost of approximately \$1 per pound.

2. Lubkin, V., and Carsten, M.: Elimination of Dehydration in Histological Technique, *Science* 95:2477 (June 19) 1942.

3. Downs, W. G.: Polyvinyl Alcohol: A Medium for Mounting and Clearing Biological Specimens, *Science* 97:2528 (June 11) 1943.

our stock solution of polyvinyl alcohol, generally, in accordance with the directions given by Downs. Fifteen grams of "PVA" (grade RH-349) powder is added slowly to 100 cc. of cold water in a beaker. The mixture is then stirred and heated in a water bath at a temperature of about 80 C. The heating process is continued until the solution attains the viscosity of thick molasses. Should undissolved clumps or particles remain, the solution is filtered through two layers of cheese cloth into a beaker. At this stage the solution may appear milky because of the inclusion of small air bubbles, but it later clears on further heating or standing. This stock solution may be stored for future use, after having been prepared in quantity.

By the addition of lactic acid and phenol to the stock solution of polyvinyl alcohol, Downs prepared a mounting medium which not only dehydrates but clears the specimen to be mounted in a satisfactory manner and hardens to provide a solid hyaline mount which requires no sealing in, as does a liquid mount. The use of this medium obviates the necessity for dehydration as in mounting in balsam or similar material. This is the mounting medium which we have used in our work. It is prepared by combining "PVA" stock solution 56 per cent, phenol 22 per cent and lactic acid 22 per cent by volume. In mixing, the lactic acid must be added first to the "PVA" stock solution before phenol is added, otherwise the "PVA" will change into a soft white sticky mass. In the mounting of cutaneous fungi we have added cotton blue dye to the lactophenol plastic in the proportion of 0.05 per cent. The dye provides a satisfactory degree of contrast in showing up fungus structures.

The "PVA" lactophenol medium is rapid and simple in use. The material to be mounted is placed on a clean dry grease-free glass slide, and a small quantity of the plastic is added, either the colorless medium or a medium to which the cotton blue dye has been added, and a cover slip is pressed into place. It is desirable to have some of the mounting medium flow out around the edges of the cover slip, as this aids in the sealing process. Within twenty-four to forty-eight hours excellent clearing of the specimen will have taken place and the specimen will be sealed in a semihard clear mount. A considerably longer period of time is required, however, before the plastic becomes completely hardened throughout and permanent in nature. Preparations may be handled and examined safely before complete hardening has taken place.

In the mounting of material removed from fungus cultures, a small amount of the agar containing the fungus is removed from the culture and placed on a slide, and the "PVA" lactophenol is caused to flow over and about it. If the cotton blue medium is used it is allowed to remain in contact with the fungus for thirty to sixty seconds before the cover slip is added, in order to allow the fungus structures to absorb

the stain. The dehydrating and clearing action of the medium takes care of the agar and its water content satisfactorily, and a permanent mount is provided for the fungus as it grows *in situ*. In slide cultures it is often possible to mount the fungus intact as it grows in culture by cutting out a thin section perpendicular to the surface. A convenient "knife" for the removal of such material from fungus cultures is provided by sealing a small piece of triangular-shaped platinum foil into the end of a solid glass stirring rod, which has been previously softened in a Bunsen flame.<sup>4</sup> A useful functional tool for the transfer of fungus material can be made from an inoculation needle inserted into a bacteriologic loop handle. The tip of the needle is heated in flame and bent about 4 mm. to a right angle.

Semitransparent mounts of scrapings of skin to demonstrate fungi may be prepared by transferring such scrapings directly from 70 per cent alcohol to the lactophenol plastic. While clearing is not as rapid nor as complete as with sodium hydroxide, a preparation is obtained in which the fungus structures may be readily seen. Only thin scales may be used with this method.

This mounting material, however, has its greatest field of usefulness in the making of permanent preparations from material removed from slide cultures and from ordinary fungus cultures growing on agar slants or on Petri culture dishes. In mounts of small arthropods, such as *Sarcoptes scabiei* or *Phthirus pubis* and its ova, the "PVA" lactophenol clears the object producing a transparency by which the details of its anatomic structure are clearly revealed. For the small arthropods with much body thickness, hollow ground or depression slides and circular cover slips are best adapted to the making of permanent preparations with the plastic. In the preparation of all types of mounts with the material, care should be taken to add a sufficient amount of the medium initially to allow for loss of substance due to evaporation of water through drying during the first few days.

#### SUMMARY

A plastic medium, polyvinyl alcohol with lactophenol, is described, which dehydrates and clears specimens and forms easily prepared, permanent, hard, hyaline mounts for the preservation of fungi and small arthropods of interest to dermatologists.

4. Dr. Ethel M. Rockwood made this suggestion.

## **ACRODERMATITIS PUSTULOSA PERSTANS (SO-CALLED PUSTULAR PSORIASIS)**

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**AND**

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**AND**

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**BROOKLYN**

**I**N A RECENT article<sup>1</sup> histologic evidence was offered to show that the majority of cases of so-called pustular psoriasis were not related to psoriasis. We are reporting 11 additional cases to corroborate this view. In each of the 11 patients the eruption was limited to the palms, soles or both, and in no case was there a personal history or any clinical observations of psoriasis. In each case the microscopic picture was the same. In all the cases the Wassermann and Kahn reactions of the blood were negative, the urine was normal, no significant abnormalities were revealed in mycologic examinations and no foci of infection were detected.

### **REPORT OF CASES**

**CASE 1.**—W. T., a white man aged 34, reported at the skin and cancer clinic in 1943 with a pustular eruption on the palms and soles, which had been present for eleven years with periods of remission. Roentgen rays and various ointments had been used, but with no benefit. The patient was treated while in the Navy (1941 to 1943). Clinically there were numerous discrete pustules on the palms and soles. There was no improvement after treatment with 5 per cent ointment of coal tar or with 2 per cent resorcinol and 5 per cent solution of coal tar in 70 per cent alcohol.

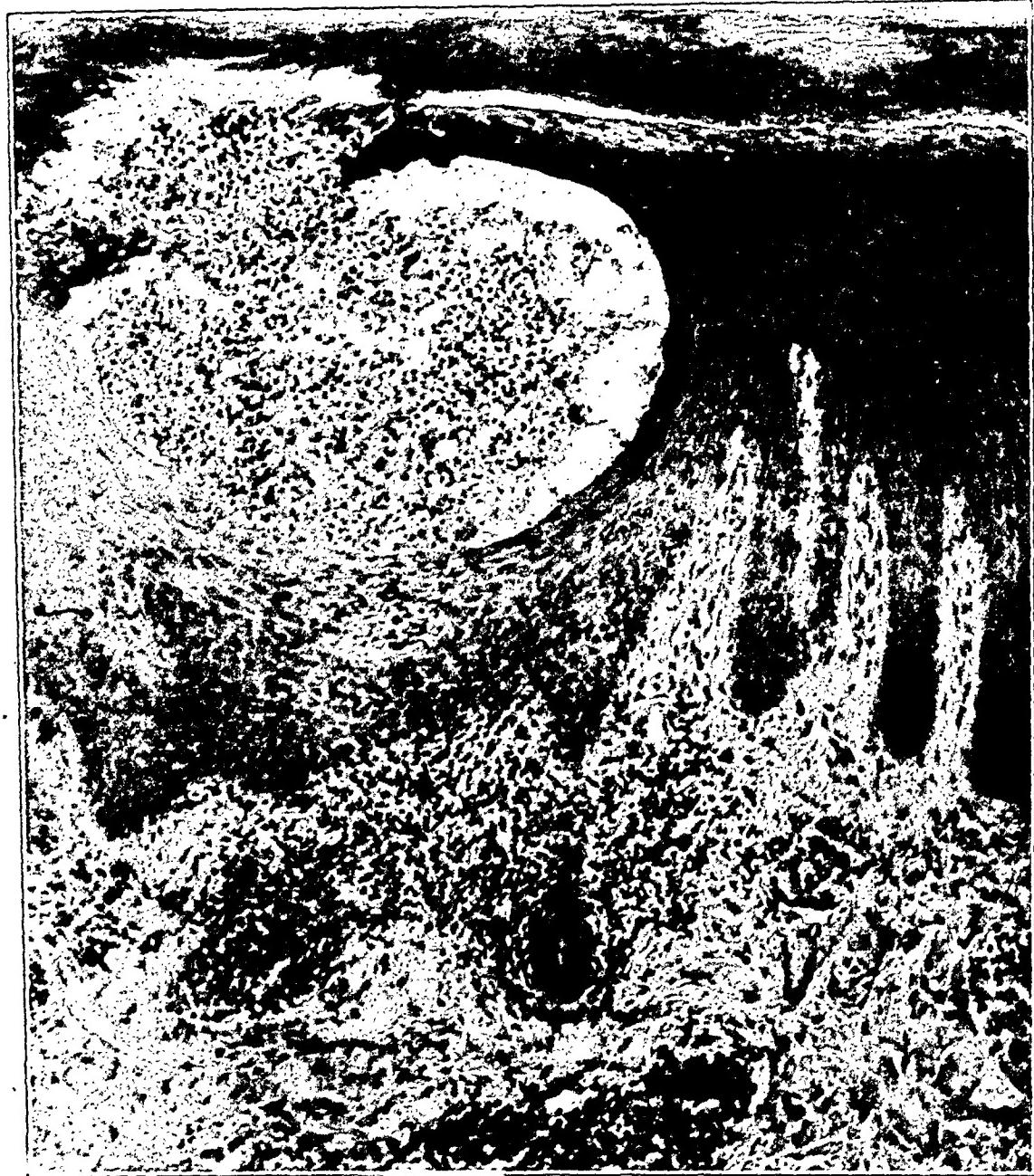
**CASE 2.**—H. A., a white man aged 53, was seen in 1939 with a pustular crusted eruption of one year's duration on the soles and left palm. During treatment with various ointments there were periods of remission. On examination in November 1945, pustular lesions were still present on the palms and soles. There was slight improvement from treatment with 5 per cent ointment of coal tar.

**CASE 3.**—S. F., a white man aged 45, was seen in 1939 with numerous isolated pustular lesions of six months' duration on the palms and soles. There were a few scaly lesions. There was no response to therapy with 10 per cent naphthalan,

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1. Sachs, W., and Scannone, F.: So-Called "Pustular Psoriasis," *J. Invest. Dermat.* **6**:349 (Dec.) 1945.



Photomicrograph showing a pustule within the epidermis and inflammatory reaction in the upper part of the cutis below the pustule.

5 per cent ammoniated mercury, 3 per cent salicylic acid, 5 per cent ointment of coal tar and resorcinol ointment.

CASE 4.—S. D., a white woman aged 45, was seen in 1939 with a pustular eruption of fifteen years' duration on the palms and soles. She had had a few periods of remission, but the present attack had persisted for over one year. The patient's mother had psoriasis. Treatment with 30 per cent sulfur ointment produced no improvement. However, there was some improvement from treatment with 5 per cent ointment of coal tar.

CASE 5.—F. M., a 46 year old white man, reported at the clinic in 1939 with a pustular eruption of a few months' duration on the palms and soles. Treatment

with coal tar, 30 per cent sulfur ointment and 0.5 per cent chrysarobin ointment resulted in no improvement.

CASE 6.—S. K., a white woman aged 40, had had a pustular eruption on the palms and soles, especially the heels, for the past seven years. On the palms were small isolated pustules, while on the soles there were large crusted pustular tender lesions. The lesions did not respond to 5 per cent ointment of coal tar. She had had one spontaneous remission two years previously, which lasted for one year.

CASE 7.—R. F., a 44 year old white man, was seen at the clinic in 1938. For one year there had been a pustular eruption on his palms and soles. The eruption did not respond to therapy, except that slight improvement occurred from treatment with 30 per cent sulfur ointment and 5 per cent ointment of coal tar.

CASE 8.—S. L., a 26 year old white man, entered the clinic with a pustular eruption on the palms and soles, which had persisted for one year. His history showed that the disease had developed while he was in the Army but that it had become more widespread soon after his discharge from the service. On examination, an erythematous pustular eruption was seen covering the palms, especially on the thenar eminences, and on the soles. Five per cent ointment of coal tar was ineffective. After an attack of influenza with fever the eruption improved somewhat.

CASE 9.—R. R., a white man aged 64, entered the clinic in 1942, complaining of an eruption on the posterior surfaces and tips of both large toes and on the left sole. He had had the dermatosis for the past twenty years, with periods of exacerbations and remissions. Examination disclosed small pustules on the tips and posterior aspects of the distal phalanges of both big toes. There were some scales, which seemed to be remnants of previous pustules. The nails of the affected toes were thickened, and there were similar lesions on the mesial aspect of the left sole. The patient had been treated with 5 per cent chrysarobin ointment, ointment of benzoic and salicylic acid and weekly doses of unfiltered roentgen rays (75 r) totaling 1,200 r, with no improvement. There had been definite improvement while he used a 5 per cent ointment of coal tar.

CASE 10.—M. B., a 44 year old white woman, was seen in the clinic in 1940 with an extensive pustular eruption, with crusting on the palms and soles. The duration had been five months. She presented a slight roughening of the elbows and knees, but no definite evidence of psoriasis. She was seen only once.

CASE 11.—M. K., a 47 year old man, was seen in the clinic in 1939 with a vesiculopustular eruption on the soles, especially the heels. He had had the eruption for four years, with the usual remissions. The patient improved slightly and temporarily while using ointment of lead oleate.

#### COMMENT

The eruption in each of the 11 patients was identified clinically as so-called pustular psoriasis by various members of the staff of the New York Skin and Cancer Unit and by one of us (G. M. M.). It was agreed that there was no clinical evidence or personal history of psoriasis in any case. In 1 instance the patient's mother had psoriasis. There was no psoriasis in the family history of 10 patients.

As is well known and as discussed by Sachs and Scannone<sup>1</sup> and others, there has been considerable controversy relative to the nosologic position of this disease. On histologic grounds one of us (W. S.)

has always contended that the disease is not psoriasis, while another (G. M. M.), largely on clinical grounds, had until recently believed that all cases represented an aberrant form of psoriasis.

The principal clinical characteristics of the disease are briefly as follows: The disease usually persists for a few years or many years, and there are spontaneous remissions and exacerbations. During remission there may be few or no elementary lesions, but the skin usually remains excessively dry, parchment-like and perhaps slightly scaly. The elementary lesion is a pustule, although at the beginning of an exacerbation it may be a vesicle, which soon becomes a pustule. The pustules are sterile, and they are distributed over any or all parts of the palms, soles, fingers and toes. Their predilection is for the thenar portion of the palms and the center of the soles, extending to the inner side of the feet.

As a rule the eruption is recalcitrant to all therapy. The disease in some patients responds favorably to the Goeckerman treatment. Some patients recover after the removal of a focus of infection, as a result of treatment with autogenous bacterial vaccine, or after a combination of both types of therapy. We believe that in many instances there is a spontaneous permanent cure, although the skin of the affected areas may remain parchment-like for many years after exacerbations of elementary lesions have ceased.

Some patients with the disease have psoriasis on other parts of the body, and the histologic architecture of the palmar and solar lesions is either definitely that of psoriasis or is compatible with it. Such cases may be designated as of psoriasis pustulosa or psoriasis with pustules. At times pustular psoriasis may be limited to the palms and soles. In such cases the diagnosis can be established only by a biopsy. Because some are cases of psoriasis, one of us (G. M. M.) had thought that all cases represented psoriasis, regardless of the histologic picture. As shown by Andrews and Machacek,<sup>2</sup> there are cases in which the eruption disappears after the removal of a focus of infection (pustular bacteride) and in which the histopathologic structure is not that of psoriasis.

It now appears that there may be three groups which may be clinically identical. The pustular bacteride may represent a small group. Pustular psoriasis certainly represents another small group. We now believe that the numerically largest group represents neither psoriasis nor a bacteride, but that it is an entity. The 11 cases herein reported belong to the last group. We offer the term acrodermatitis pustulosa perstans for the entity. The name is selected because the eruption is limited to the palms and soles, the pustules are of prime importance and the

2. Andrews, C., and Machacek, G. F.: Pustular Bacterids of the Hands and Feet, *Arch. Dermat. & Syph.* 32:837 (Dec.) 1935.

eruption is persistent. Audry,<sup>3</sup> in 1900, called the disease acrodermatitis perstans because he thought that it was a form of *les acrodermatitides continues de Hallopeau*.<sup>4</sup> This concept has long been discarded.

Should it be accepted, the term pustular psoriasis may be reserved for psoriasis with pustules, regardless of location.

#### SUMMARY

Eleven cases of so-called pustular psoriasis are reported. All have exactly the same clinical and microscopic features. There was no evidence of psoriasis either clinically or microscopically, and with 1 exception there was no family history of psoriasis. The name acrodermatitis pustulosa perstans is suggested for what we believe may be regarded as an entity. The cause is unknown.

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## NINTH DAY ERYTHEMA SHOWING PHOTOSENSITIVITY

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**R**EPORTS on early erythema occurring after injection of arsphenamine began to appear in the European literature<sup>1</sup> shortly after the introduction of this type of treatment. But Milian<sup>2</sup> was the first to describe it under the name of "erythema of the ninth day" as an entirely separate entity which differs significantly from true arsphenamine dermatitis. He explained this syndrome on the basis of biotropism, i.e., the ability of certain drugs to stimulate latent micro-organisms to activity. According to Milian ninth day erythema is weakened measles, rubeola or scarlet fever, the micro-organisms of which were mobilized or the immunity to which was temporarily disturbed by arsphenamine. In fact, these types of erythema, with their generally morbilliform or scarlatiniform eruptions usually accompanied with constitutional symptoms, frequently simulate these acute infectious diseases. Yet Milian's theory was not accepted by most writers. Schreiner,<sup>3</sup> obtaining positive reactions in Prausnitz-Küstner passive transfer tests (thus far not confirmed by other investigators) suggested an allergic origin. Gjessing<sup>4</sup> and Cañizares and Thomas<sup>5</sup> incriminated the irritation of the autonomic nervous system in the causation of the syndrome. Keim<sup>6</sup>

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From the Department of Dermatology, Hadassah Municipal Hospital.

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4. Gjessing, H. C.: A Form of Salvarsan Dermatitis (Ninth Day Erythema) in Which Salvarsan Treatment Is Continued, Acta dermat.-venereol. **9**:185, 1928.

5. Cañizares, O., and Thomas, E. W.: Early Acute Arsenical Erythemas: A Study of Eleven Cases of the "Erythema of the Ninth Day" of Milian, Arch. Dermat. & Syph. **39**:867 (May) 1939.

6. Keim, H. L.: "Erythema of the Ninth Day" Following Administration of Arsphenamine: Preliminary Report, Arch. Dermat. & Syph. **31**:291 (March) 1935.

incriminated not the arsenical but the phenol content liberated from the drug. Wainstein and Smelov,<sup>7</sup> reviewing 30 cases from Moscow, which were approximately 1 per cent of all their cases in which treatment was with neoarsphenamine, expressed the opinion that the cause of the syndrome is not uniform. Likewise, most authors do not agree with Milian that arsphenamine can be given with the same or even larger doses during the development of erythema. On the contrary, the recent general view of syphilologists is that caution should be exercised and that specific treatment be stopped. This caution is especially justified because, as Sweitzer<sup>8</sup> and Trow<sup>9</sup> rightly emphasized, the differentiation between ninth day erythema and true arsphenamine dermatitis is not always possible with certainty. Peters,<sup>10</sup> reporting 54 cases, concluded that arsphenamine should be withheld for at least one month after the recovery from the syndrome and treatment with it should then be resumed with smaller doses.

Of a number of cases of ninth day erythema which I have encountered, 2 that were recently seen were distinguished by their peculiar clinical course and particularly by the erythema's being confined only to the uncovered areas.

#### REPORT OF CASES

CASE 1.—Mr. V. Y., aged 41, who had emigrated to Palestine from Poland in 1924, was referred to the dermatologic clinic of the Hadassah Municipal Hospital for antisyphilitic treatment. His past history revealed that twenty-one years previously, while he was a soldier, he had received a course of treatment for approximately two months, consisting of intramuscular and intravenous injections for a penile sore. Three years later he married. His wife and three children remained healthy. In 1940 he voluntarily joined the British Army and served three years in Egypt and Libya. He was recently discharged from the army because of chronic rheumatic pains and a positive Wassermann reaction.

On Nov. 8, 1943, antisyphilitic treatment was instituted. On November 22, after receiving five injections of bismuth subsalicylate and two of neoarsphenamine and exactly nine days after the first injection of 0.45 Gm. of neoarsphenamine, a rash appeared on the neck and the upper extremities which became more pronounced in a few days and assumed a typical erythema multiforme character. Symmetrically, on the dorsa of both hands, the external aspects of the forearms, the lower thirds of the arms and the V-shaped area of the neck there were coin-sized and coin-shaped elevated papules or plaques of a reddish lilac color. He complained of a mildly burning sensation, but no fever or systemic symptoms were

7. Wainstein, A., and Smelov, N.: Sur le question de la symptomatologie, de la pathogénie et de la thérapeutique des exanthèmes précoce arsénobenzoliques—"érythèmes du neuvième jour" de Milian, Ann. de dermat. et syph. 8:215, 1937.

8. Sweitzer, S. E., in discussion on Keim.<sup>6</sup>

9. Trow, E. Y., in discussion on Keim.<sup>6</sup>

10. Peters, E. E.: Syndrome of Milian's Erythema of the Ninth Day, Am. J. Syph., Gonor. & Ven. Dis. 25:527, 1941; abstracted, Wise, F., and Sulzberger, M. B.: The 1940 Year Book of Dermatology and Syphilology, Chicago, The Year Book Publishers, Inc., 1941, p. 611.

present. The diagnosis of ninth day erythema was made, and the medication was stopped. The patient was presented at the meeting of the dermatologic society. The eruption gradually faded, after lasting eighteen days. The specific treatment was resumed on Jan. 6, 1944 and was well tolerated.

CASE 2.—G. B., a woman aged 42, who had emigrated twenty-five years previously from Russia, came to the dermatologic clinic on May 21, 1945. She presented a sharply defined brownish red patch, 8 cm. in diameter, with circular and serpiginous outlines on the upper outer surface of the left forearms, of three years' duration, and a similar but smaller lesion on the forehead, of one-half year's duration. The clinical picture was strongly suggestive of tuberoserpiginous syphilis. Her past history revealed that she had married at the age of 16, had two miscarriages and underwent a hysterectomy. The serologic reactions (Meinecke, Kahn, Rappaport) were strongly positive. Combined bismuth compound and neoarsphenamine therapy was started.

On July 15, ten days after the first injection of 0.3 Gm. neoarsphenamine, an erythematous maculopapular eruption developed, which spread rapidly and became confluent in places. Only the uncovered areas were involved: both cheeks, the sides and anterior parts of the neck, the backs of the hands, the forearms, the lower thirds of the arms and to a lesser degree the legs. She felt perfectly well except for a mild itching. She was seen almost every day. The eruption cleared completely after a week. Three weeks later 0.15 Gm. neoarsphenamine was given; this caused nausea, but further treatment was continued with no untoward reactions.

#### COMMENT

Although the main eruption of the syndrome is morbilliform or scarlatiniform, erythema multiforme has also been observed. Of the 11 cases of Cañizares and Thomas, 2 were of the erythema multiforme type, but the lesions were located also on the back. The relatively long duration of eighteen days in the first case is noteworthy. According to Peters the maximum limit of duration is twelve days. Neither of these patients had fever or other constitutional symptoms.

As to the special localization in the 2 cases, photosensitivity to arsenicals<sup>11</sup> and also to arsphenamine<sup>12</sup> has occasionally been observed, but, as far as I know, not of the type of ninth day erythema. On the other hand, these patients were not exposed to the sunlight during the treatment. In case 1 the disease occurred in November, but the patient's skin had been exposed to the sun and was considerably tanned after

11. (a) Ayres, S., Jr., and Anderson, N. P.: Cutaneous Manifestations of Arsenic Poisoning, Arch. Dermat. & Syph. **30**:33 (July) 1934. (b) Ayres, S., Jr.: Arsenical Dermatitis and Alopecia Areata Showing Photosensitivity, ibid. **31**:263 (Feb.) 1935.

12. (a) Jadassohn, J.: Bemerkungen zur Sensibilisierung und Desensibilisierung bei den Ekzemen im Anschluss an einen Fall von Odolekzem, Klin. Wchnschr. **2**:1680, 1923. (b) Juon, M.: Strahlenüberempfindlichkeit nach generalisiertter Dermatitis infolge einer Salvarsan- und Hg-Kur, Arch. f. Dermat. u. Syph. **156**:355, 1928. (c) Stokes, J. H.; Beerman, H., and Ingraham, N. R., Jr.: Photodynamic Effects in Dermatology, Am. J. M. Sc. **203**:608, 1942.

lengthy service in the Western Desert. The second patient had fair skin, and her exposed areas were rather tanned after a twenty-five year stay in this country. In the classic cases of photosensitivity too—in pellagra, for example—it is believed that the characteristic cutaneous changes are frequently not due to direct irradiation by the sun. The skin which has been altered by the sun and light possesses a lower resistance and is more susceptible to sensitization. The damaged skin plays some role in the localization of the common arsphenamine dermatitis (Silberstein,<sup>13</sup> Keim), but no such relation is so far known in the disease under consideration. Nevertheless, the impression is that in the cases herein reported damage to the skin by the sun might be in a great degree responsible for the special localization of erythema.

#### SUMMARY

Two cases of ninth day erythema are described. The eruption, which was the only clinical manifestation of the syndrome, was strictly limited to the exposed areas. I believe that previous damage to the skin by sunlight was responsible for this special localization.

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13. Silberstein, S.: Zur Pathogenese der Salvarsandermatitis und über den Arsennachweis in der Haut nach Salversanbehandlung, Arch. f. Dermat. u. Syph. **144**:260, 1923.

# STUDIES ON SENSITIVITY TO SULFONAMIDE OINTMENTS

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MANY reports in the literature emphasize the frequent occurrence of cutaneous sensitivity following the topical application of the sulfonamide group of drugs. Darke<sup>1</sup> treated 218 patients with injuries of a minor surgical nature with a 5 per cent sulfathiazole cream and observed 12 instances in which sensitivity developed (5.5 per cent). Inges<sup>2</sup> treated 300 patients with sulfathiazole and sulfadiazine in salves, powders and lotions. Sensitivity reactions were observed in 10 patients (3.3 per cent). Robert<sup>3</sup> observed 4 cases of hypersensitivity to sulfathiazole ointment when making patch tests on 200 patients who had never been treated with sulfathiazole. Cole,<sup>4</sup> in the report for the Council on Pharmacy and Chemistry of the American Medical Association, reviewed the literature on the local use of the sulfonamide compounds in dermatology. He advised that sulfonamide drugs should not be applied locally for more than five days because of the danger of sensitization.

This study was performed to determine what percentage of a group of 200 volunteers could be sensitized to three different sulfonamide ointments. An attempt was made to test the same persons with all three ointments in an effort to determine whether sensitivity to one sulfonamide drug predisposed to sensitivity to another.

Funds and material for this study were supplied by the Lambert Pharmacal Co. Studies, observations and reports are from the Dermatological Departments of the Barnard Free Skin and Cancer Hospital and the School of Medicine, Washington University, Service of Dr. M. F. Engman Sr.

1. Darke, R. A.: Sensitivity to Topical Application of Sulfathiazole Ointment, J. A. M. A. 124:403-404 (Feb. 12) 1944.
2. Inges, A. E.: Dermatoses: Local Treatment with Sulfathiazole and Sulfadiazine, California & West. Med. 58:269-272 (May) 1943.
3. Robert, P.: Uses of Sulfonamides in Dermatology, Schweiz. med. Wchnschr. 73:627-632 (May 8) 1943.
4. Cole, H. N.: Chemotherapy in Dermatology, J. A. M. A. 123:411-417 (Oct. 16) 1943.

## OINTMENTS

The three sulfonamide ointments submitted for patch tests were: (1) a 5 per cent sulfadiazine ointment, with the ointment base adjusted to  $p_H$  7 to 7.5, (2) a 5 per cent sulfathiazole ointment,  $p_H$  7 to 7.5 and (3) a 5 per cent sulfadiazine ointment,  $p_H$  8.1, so that the sodium salt of sulfadiazine was present.<sup>5</sup> The ointment base was water miscible and contained "daxad, no. 11," a polymerized alkyl aryl sulfonate (Dewey Almy Co.); "santomerse, 3," an alkylated aryl sulfonate (Monsanto Chemical Co.); glycerine; phenyl mercuric acetate, a fungicide; glyceryl monostearate; stearic acid, triple pressed; anhydrous wool fat U. S. P.; liquid petrolatum U. S. P., sodium chloride and water.

## PROCEDURE IN PATCH TESTS

The patch tests with the sulfonamide ointments were performed according to the procedure recommended by Schwartz and Peck.<sup>6</sup> The type of test used has been designated as the "prophetic patch test" technic and is used to determine whether or not a substance will produce dermatitis after contact with the skin. Two separate tests are made ten to fourteen days apart, on the same person. Two hundred persons are used, just as in other standard studies with patch tests. It is presumed that reactions will occur in the first series if the material tested is a primary irritant, provided that the person under observation has never had previous contact with the substance. The reactions caused by the second series of tests indicate the number of persons in whom sensitivity has been induced by the first patch test.

A group of about 200 volunteers was tested with each ointment—223 for (1), 210 for (2) and 200 for (3). These volunteers were factory employees and patients at two of the St. Louis hospitals. The ages of the volunteers ranged from 16 to 70 years. The two sexes were fairly equally represented. An attempt was made to test the same persons with all three of the ointments, but this was not possible with the first sulfadiazine ointment.

The technic employed was as follows: 1. The sulfadiazine (or sulfathiazole) ointment and the ointment base, which was used as a control, were applied to pieces of gauze  $\frac{1}{4}$  inch (0.6 cm.) square and covered with standard "elastopatch" (Duke Manufacturing Company). 2. The patches were placed on the scapular and infrascapular areas, on the back of the arms and on the anterior and internal surfaces of the thighs. 3. The patches were removed approximately forty-eight hours later

5. Information supplied to us indicated that at a  $p_H$  of 7 to 7.5 only minute amounts of the sodium salts of sulfathiazole or sulfadiazine would be available.

6. Schwartz, L., and Peck, S. M.: The Patch Test in Contact Dermatitis, Pub. Health Rep. 59:546-557 (April 28) 1944.

and the areas observed. The areas were again observed in ninety-six and one hundred and twenty hours. 4. When ten or more days had elapsed after the removal of the first patches, the patches were reapplied and steps 2 and 3 repeated.

#### RESULTS

With the 5 per cent sulfadiazine ointment (base  $p_H$  7 to 7.5), 4 of the volunteers demonstrated positive reactions in the first test. Two of these volunteers gave no history of ingestion of or exposure to any of the sulfonamide drugs. The third person had experienced dermatitis after the oral administration of sulfathiazole, and the fourth had been exposed to sulfadiazine ointment in her work.

In the second test, 6 volunteers demonstrated reactions<sup>7</sup> of 1 plus to patch tests with the ointment. One of them reacted to the ointment

*Results of Tests with Sulfonamide Ointments*

Case and Subject	Sex	Sulfadiazine ( $p_H$ 7-7.5)		Sulfathiazole ( $p_H$ 7-7.5)		Sulfadiazine ( $p_H$ 8.1)	
		First Test	Second Test	First Test	Second Test	First Test	Second Test
1 V. J.....	F	+	—	..	..	..	..
2 E. S.....	F	+	—	..	..	..	..
3 M. A.....	F	+*	..	..	..	..	..
4 O. A.....	M	+†	..	..	..	..	..
5 E. S.....	F	—	+	..	..	..	..
6 E. L.....	F	—	+	..	..	..	..
7 B. O.....	F	—	+	..	..	..	..
8 J. A.....	M	—	+	..	..	..	..
9 F. K.....	F	—	+	..	..	..	..
10 S. A.....	F	—‡	+‡	..	..	..	..
11 A. K.....	F	—	..	++	—	—	—
12 P. B.....	M	..	..	++	—	++	—
13 L. B.....	F	—	—	—	+	—	—

\* This subject had contact with sulfadiazine.

† This subject had a cutaneous eruption after taking sulfathiazole orally.

‡ S. A. reacted to the base.

base to the same extent as to the ointment base plus the sulfadiazine, and results for this subject are not included in the final tabulation.

With the 5 per cent sulfathiazole ointment (base  $p_H$  7 to 7.5), 2 volunteers demonstrated positive reactions in the first test. None of these reacted to the ointment base. There was no history of exposure to sulfathiazole in these 2 volunteers, and on further testing (with the sulfadiazine ointment base  $p_H$  8.1) 1 of these demonstrated positive and 1 negative reactions.

In the second test only 1 volunteer had a positive reaction to the sulfathiazole ointment and not to the base. This volunteer had been tested with both sulfadiazine ointments with no reaction.

7. One plus was a reaction of erythema, 2 plus erythema and edema, 3 plus erythema, papules and a few vesicles and 4 plus erythema, edema, many vesicles and, in some cases, ulceration.

With the 5 per cent sulfadiazine ointment (base  $p_H$  8.1), only 1 volunteer demonstrated positive reactions to this sulfadiazine ointment in the first patch test. He reacted to the 5 per cent sulfathiazole ointment in the same manner. He denied any exposure to sulfonamide drugs.

None of these volunteers reacted in another patch test with this sulfadiazine ointment.

#### COMMENT

The number of persons sensitized to the sulfonamide ointments by means of patch tests was small. Only 2.3 per cent were sensitized to the first sulfadiazine ointment; none were sensitized to the second sulfadiazine ointment, and 0.49 per cent were sensitized to the sulfathiazole ointment. A higher percentage of sensitizations to the sulfonamide drugs was observed by others<sup>8</sup> who were using sulfonamide ointments in the treatment of superficial infections and injuries. However, in the patch test the material is applied only once, in only a small amount and to one area of the skin. Under actual conditions of use of such an ointment the opportunity for sensitization may be much greater, as the ointment may be applied several times during the day and over large surfaces. The actual area exposed in such applications might be a factor in cutaneous sensitization. Further work should be done to determine whether the amount of the drug, the frequency of application and the area of surface to which it is applied play any part in the frequency of sensitization to the sulfonamide drugs.

It was hoped that something would be learned about the frequency of cross reactions from different sulfonamide drugs. However, there were not enough sensitive volunteers available for further testing to permit us to determine the frequency of such reactions.

#### SUMMARY

A group of 223 volunteers was given patch tests with a 5 per cent sulfadiazine ointment (base  $p_H$  7 to 7.5). Two hundred and ten volunteers had patch tests with a 5 per cent sulfathiazole ointment (base  $p_H$  7 to 7.5). Two hundred volunteers had patch tests with a 5 per cent sulfadiazine ointment (base  $p_H$  8.1). Of these volunteers 2.3 per cent were sensitized to the first sulfadiazine ointment; 0.49 per cent were sensitized to the sulfathiazole ointment, and none were sensitized to the second sulfadiazine ointment.

#### CONCLUSIONS

In view of the many clinical reports on sensitivity to the sulfonamide drugs, we are not sure that the results reported here are valid. It is

8. Darke.<sup>1</sup> Inges.<sup>2</sup>

our feeling that epithelial sensitization may take place with greater facility when the sulfonamide drugs are used on previously inflamed skin and over larger areas of surface.

It is pertinent that probably hundreds of thousands of persons have been treated locally with the sulfonamide drugs, while, perhaps, only a few thousands have shown phenomena of cutaneous sensitization. We are, therefore, inclined to change the views which we had previously expressed, namely, that the sulfonamide drugs are highly potent cutaneous sensitizers. We would like to qualify that opinion by saying that the sulfonamide drugs are probably highly potent sensitizers when they are applied over relatively large areas of skin and particularly on damaged skin. Moreover, we believe that when the sulfonamide drugs are used on the skin for more than five days the probability of sensitization is greatly increased.

## SUPPURATIVE RINGWORM CONTRACTED FROM CATTLE

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DURING the past three years, we have observed a series of 23 cases of deep suppurative ringworm infections which were contracted from cattle. In the large majority of the cases the organisms were difficult to isolate and produced slowly growing, glabrous colonies which were identified as belonging to the faviform group of trichophyta. In a few cases the rapidly growing, fluffy colonies of the gypseum trichophyta were obtained.

Since the lesions were of a deep suppurative character—a type of trichophyton infection which, according to Conant and his colleagues,<sup>1</sup> is rarely seen in this country—and since the incidence of the transmission of ringworm infection from livestock to farm workers is not generally known or recognized, we feel that these cases should be reported. Also the high incidence of the faviform trichophyta observed in these infections and the difficulty encountered in their isolation and identification emphasize the importance of a study of these organisms as causative agents of animal ringworm which may be transmitted to man.

According to Hagan,<sup>2</sup> ringworm is a common disease of cattle in this country and especially of their young, and human infection occasionally occurs. The chief cause of ringworm in cattle appears to be the common ectothrix trichophyton, Trichophyton mentagrophytes, or other members of the gypseum group. However, the faviform trichophyta, Trichophyton album, Trichophyton discoides, Trichophyton ochraceum and Trichophyton verrucosum are known to be causative

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1. Conant, N. F.; Martin, D. S.; Smith, D. T.; Baker, R. D., and Callaway, J. L.: Manual of Clinical Mycology, Military Medical Manual, National Research Council, Division of Medical Sciences, Philadelphia, W. B. Saunders Company, 1944.

2. Hagan, W. A.: The Infectious Diseases of Domestic Animals, Ithaca, N. Y., Comstock Publishing Company, 1943.

agents of ringworm in cattle and horses.<sup>3</sup> Most of the veterinary literature indicates that ringworm infection of cattle and horses may occasionally be transmitted to man, but the incidence of this type of infection in the United States is not generally known. In 1938, Gammel and Work<sup>4</sup> reported that during a period of fourteen years they observed only 4 cases of ringworm which had been contracted from livestock. Cultural studies showed that the infection in 3 of these cases was caused by *Trichophyton gypseum*, and in 1 case (apparently contracted from "scabby" sheep) was caused by one of the faviform trichophyta, *T. album* (var. *singulare*).

Human infection with the faviform trichophyta was first observed in France by Sabouraud in 1893.<sup>5</sup> During his career Sabouraud reported only 9 cases. Sporadic reports have come chiefly from Western Europe, the Balkans and North Africa. The incidence of the infection in Yugoslavia appears to have been relatively high. Georgjević and Milochevitch<sup>6</sup> observed *T. album* to be a causative agent in 81 of 241 cases of dermatomycoses in that country. The disease has been reported from Uruguay<sup>7</sup> and Mexico.<sup>8</sup> In 1934 Davidson, Gregory and Birt<sup>9</sup> reported 28 cases from Canada, and in 1938 Gammel and Work<sup>4</sup> reported 1 case in the United States. In all of the cases the source of infection was believed to be livestock.

The most common type of lesion described in human infections with the faviform trichophyta is of a suppurative character and includes all the lesions which attack the deeper layers of the skin and the hair follicles, producing nodules with suppuration. Other types of lesions, however, have been reported. The first lesion described by Sabouraud<sup>10</sup> was a flat plaque on the glabrous skin, with an impetiginized surface and flat crusts. He also described lesions resembling plaques of sebor-

3. Hutyra, F., and Marek, J.: Special Pathology and Therapeutics of Diseases of Domestic Animals, ed. 4, London, Ballière, Tindall & Cox, 1929, vol. 3.

4. Gammel, J. A., and Work, J. L.: Sycosis Parasitica Due to Favotrichophyton Album Var. Singulare, Arch. Dermat. & Syph. 38:756-772 (Nov.) 1938.

5. Sabouraud, R.: Contribution a l'étude de la trichophytie humaine, Ann. de dermat. et syph. 4:814-835, 1893.

6. Georgjević, G., and Milochevitch, S.: Aspects cliniques de trichophytie et de favus provoqués par le *Trichophyton faviforme album*, Ann. de parasitol. 13:243-252, 1935.

7. Mackinnon, J. E.: Epizootia de tiña en caballos y contaminación del hombre, Arch. urug. de med., cir. y especialid. 8:498-502, 1936.

8. Ochoterena, I.: Une nouvelle espèce de champignon producteur de teignes sabouraudites (aleurocloster) ueniae octerena, Rev. mex. biol. 4:94-100, 1924.

9. Davidson, A. M.; Gregory, P. H., and Birt, A. R.: Clinical and Mycological Study of Suppurative Ringworm, Canad. M. A. J. 31:587-591, 1934.

10. Sabouraud, R.: Les trichophyton faviforme, Ann. de dermat. et syph. 9:609-635, 1908.

rheic dermatitis and young lesions which were dry and leathery in appearance. One case, illustrated in "Les teignes,"<sup>11</sup> presented well defined, round plaques with erythematous vesicular borders and white scaly centers which become confluent, forming large polycyclic lesions. Georgjević and Milochevitch<sup>6</sup> described a clinical type of lesion due to *T. album*, which they stated was clinically identical with the lesion typical of classic favus infection.

The common ectothrix trichophyta of the gypseum group are known to produce both a superficial and a deep type of cutaneous infection. The superficial type, the most commonly seen, presents oval, round or annular scaling lesions, usually clear in the center and surrounded by a vesicular border. The deep type of infection is characterized by suppurative lesions of the sycosis, kerion or agminate folliculitis types.

#### REPORT AND SUMMARY OF CASES

The 23 cases of suppurative ringworm which we have observed (1942 to 1945) occurred in a community of farming families in central Pennsylvania. In all instances there was a history of recent contact with cattle, and in all but 5 cases the patients had observed ringworm lesions on the animals. Three cases were contracted secondarily from members of the family previously infected from the cattle.

Cultural studies indicated that 14 of the 23 cases had been caused by faviform trichophyta, 12 cases by *T. discoides* and 2 cases by *T. album*. Four cases yielded the common gypseum type of trichophyton, *T. mentagrophytes*. In the remaining 5 cases in this series, no parasitized hairs were observed and no cultures that were positive for fungi were obtained. However, the nature of the lesions, the absence of bacterial infection and the history of contact with ringworm-infected cattle indicated that the 5 cases also were of ringworm contracted from cattle.

The lesions presented were all of a deep suppurative type. They occurred, in order of frequency, on the neck, face, wrists, forearms and in the occipital region of the scalp. The cases in this series may be roughly divided into three groups: the parasitic sycosis type, or suppurative ringworm of the bearded areas of the face and neck, the kerion type, observed on the scalp and also on the bearded areas of the face and neck, and agminate folliculitis, or suppurative lesions of the glabrous skin. In the following report the general characteristics of each type of lesion are described and 2 rather atypical cases are presented in detail.

*Parasitic Sycosis.*—Seven of the patients observed presented deep suppurative lesions of the bearded areas of the face and neck. The

11. Sabouraud, R.: *Les teignes*, Paris, Masson & Cie, 1910, vol. 3.

infections started as follicular pustules, which later formed large firm nodular abscesses with thick gummy crusts, through the openings of which heavy pus could be expressed. The hairs were easily removed from the lesions, and few hairs remained in the older lesions. The majority of the patients felt no pain. Aside from the local discomfort which the lesions produced they felt well and were otherwise in good health. Two patients who had extensive involvement of the face and neck presented lesions also on the upper part of the chest and forearms. *T. discoides* was isolated in 4 of the cases. (A coexisting infection with *Streptococcus hemolyticus* was observed in 1 case.) *T. album* was isolated in 1 case and *T. mentagrophytes* in 1 case. In the remaining case cultures were negative for both bacteria and fungi.

One case in this group did not present the typical suppurative lesions when first seen. The patient stated that for three weeks he had noticed a "redness" which

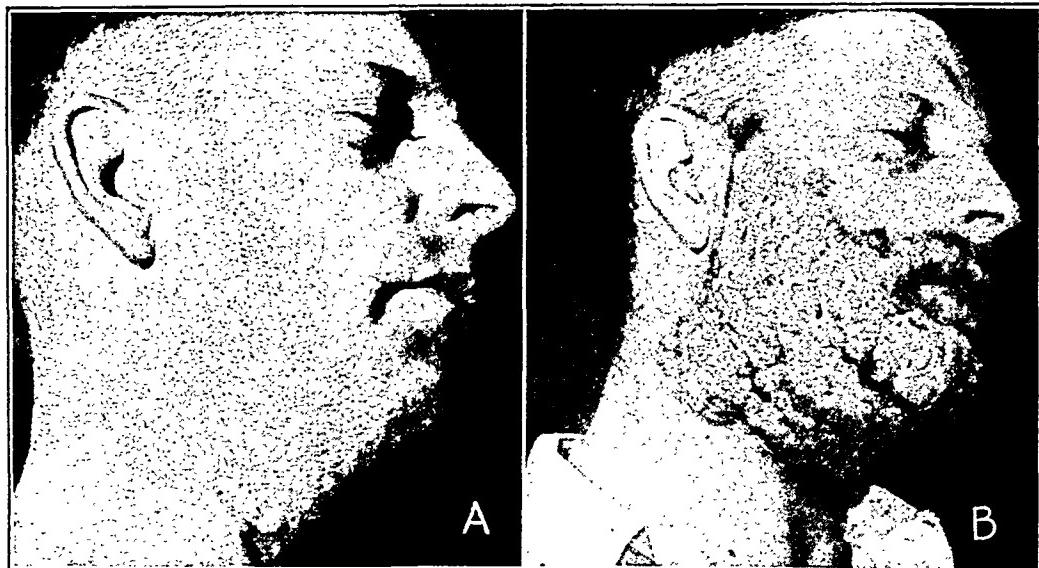


Fig. 1.—Parasitic sycosis caused by *T. discoides*. *A*, early stage in which superficial ringworm preceded the development of deep suppurative lesions. *B*, later stage in which suppurative lesions are well developed.

had appeared at the site of an acid burn on the left side of the neck. The erythema spread over both sides of the neck and face after the burn itself had healed. In these areas there developed many raised, annular and polycyclic lesions, typical of superficial ringworm (fig. 1). No vesicles were observed at the borders, although the patient stated that he had had vesicles in these areas. He had a small coin-sized lesion in the left sternoclavicular area. (These lesions appeared to be similar to those described by Sabouraud in a case due to *T. album*.<sup>11</sup>)

Examination of scales from the borders of the lesions and of hairs from these areas did not reveal any spores or mycelial elements. Three per cent ammoniated mercury was applied. After a week the whole process had improved and some of the areas had healed completely. However, several pustules had appeared on one side of the face. Five days later he had more pustules, and in front of the left ear there was an area 5 cm. in diameter with many red, deeply infiltrated pustules.

Examination of hairs, scales and pus from these affected areas still did not reveal any spores or mycelial elements, but because of the nature of the lesions and the fact that this patient was a farmer and cared for cattle, it was suspected that he was experiencing the deep suppurative type of ringworm infection which had been observed in other patients. The patient was given 2 Gm. of sodium iodide intravenously, 10 drops of sodium iodide was to be taken orally three times a day, and ointment with 20 per cent sulfathiazole sodium was prescribed for local application.

Four days later the patient returned with enormous swelling of the face. The oral temperature was 102 F, the white blood cell count was 21,000, and the patient was obviously ill. He had difficulty in eating, because of the swelling and pain in his face, and had not been able to sleep. The bearded area of the face was now covered with heavy gummy crusts, from under which thick creamy pus was oozing at many points. When pieces of the crust were removed many large pustules were observed. At this point the eruption was typical of the deep suppurative ringworm which we had previously observed, except that the process was more extensive and the patient was decidedly ill (fig. 1 B). Smears of the pus now showed many large gram-positive spores, some of which occurred in short chains. A large number of hairs were examined in sodium hydroxide preparations, but only a few were observed to be parasitized. These showed large-spored, ectothrix parasitism. Cultures of hairs and pus were made, and typical colonies of *T. discoides* were obtained. There was no evidence of bacteria infection either in the smears or in cultures of the pus made on blood agar plates.

A few days after the onset of this extensive eruption, a faint pink, macular eruption developed on the flexor surfaces of the forearms and the inner surfaces of the thighs. This disappeared spontaneously in a week. The treatment with iodides was continued and the patient gradually began to improve. After three weeks of treatment the white blood cell count fell and the temperature returned to normal. There were still many pustules, but the pus could be expressed more easily, and there was much less swelling of the face and chin. Treatment with the sulfathiazole ointment was then discontinued, but the patient was still given 2 Gm. of sodium iodide orally. Three months after the first appearance of the pustules the improvement was great. There were only a few pustules, a few large plugs and a number of small comedos. There were reticular scars throughout the subcutaneous tissue, and in a few areas there were fibrous nodules. Cultures were negative.

Another patient in this group presented lesions which were complicated by bacterial infection. There was a history of swelling of the lower part of the right cheek of a month's duration. He had had frequent contact with infected cattle, which he described as being "covered with flat white scabby sores about the eyes and mouth." He stated that he had cured several small lesions on himself with tincture of iodine.

He presented a large red indurated lesion on the right side of the chin, with many openings through which pus exuded. The lesion measured 7 cm. in diameter, and the whole surface was covered with a honey-colored exudate. There were several small superficial lesions about the face with thick, "stuck-on," honey-colored crusts. His oral temperature was 100 F., and his white blood count 20,700. He appeared tired and ill, and the whole face was swollen. Smears of the pus showed many gram-positive cocci in chains and large gram-positive spores, which occurred singly or in short chains. Culture of the pus on blood agar revealed a hemolytic streptococcus and a fungus which was identified as *T. discoides*. The patient was

treated with sulfathiazole, 1 Gm., every four hours, and 5 per cent sulfathiazole ointment was used locally. Three weeks after the first visit the swelling and tenderness subsided and there were no pustules remaining. The oral temperature was normal, the white blood count had fallen to 9,000, and cultures were negative for both bacteria and fungi.

*Kerion Lesions.*—Seven of the patients observed presented kerion lesions on the bearded areas of the face, in the hairy parts of the posterior cervical region and in the occipital region of the scalp (fig 2). The lesions of the scalp all occurred in children between the ages of 4 and 11. The kerions in the posterior cervical region and on the face occurred in men. The lesions appeared as large boggy masses which arose abruptly from the surrounding tissues. They were dark red

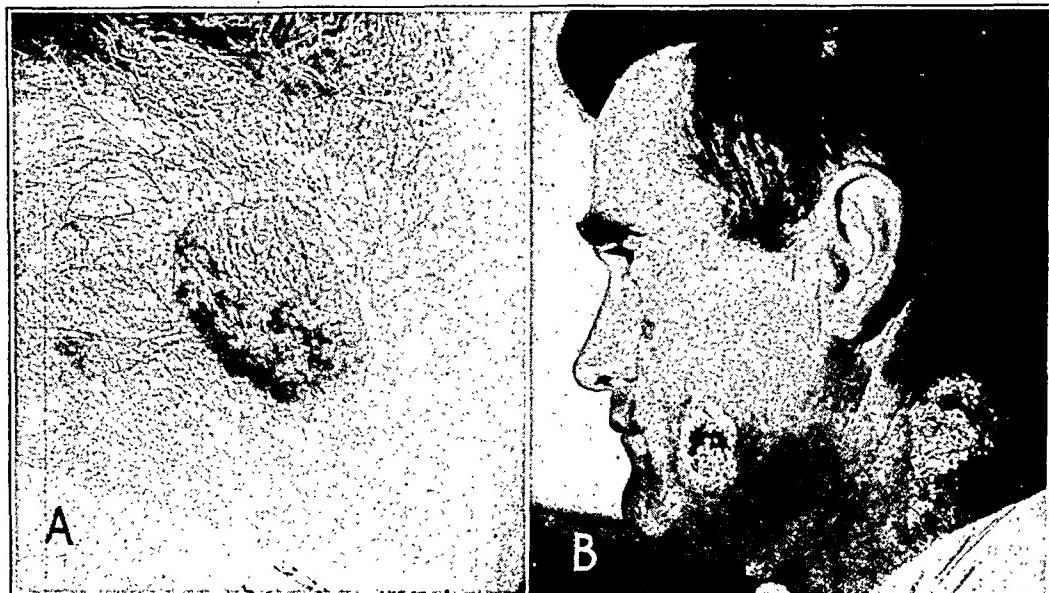


Fig. 2.—Kerion lesion produced by *T. discoides*; *A*, of the posterior cervical regions, and *B*, of the posterior cervical region and cheek.

and dotted with perifollicular abscesses. The hairs were lusterless and broken off, and in some instances they had been shed completely. In 6 cases *T. discoides* was isolated. In 1 case no parasitized hairs were observed and no fungi or bacteria were obtained from cultures. The lesions of the scalp were healed much more slowly than the lesions of the less hairy areas of the skin.

*Agminate Folliculitis of the Glabrous Skin.*—Fourteen patients sustained suppurative lesions of the glabrous skin. These occurred chiefly on the wrists and forearms (fig. 3). Five in this group also had suppurative lesions of the bearded areas or of the scalp. All of the lesions of the glabrous skin were characterized by groups of dark red nodules dotted with perifollicular pustules. Many of the hairs were loose. Pus

could usually be expressed from the lesions by gentle pressure. In no case, however, did the lesions show the deep suppurative sinuses observed in the lesions of the scalp or the heavy gummy crusts observed on the face. In 1 of the patients, who had had a lesion on the extensor surface of the forearm for a period of six weeks, numerous small vesicles developed over the fingers of both hands. These, it was concluded, were probably trichophytids. They disappeared spontaneously in a week. Cultures from the lesions of the glabrous skin were not as successful as from the more inflammatory lesions of the beard or scalp. However, in 6 cases *T. discoides* was isolated. In 3 cases *T. mentagrophytes* was obtained.



Fig. 3.—Agminate folliculitis. Lesion of extensor surface of right forearm, caused by *T. discoides*.

#### TREATMENT AND CLINICAL COURSE OF THE INFECTIONS

Local treatment of the lesions with such remedies as 3 per cent ammoniated mercury, merthiolate ointment, 1 to 2,000, and 5 per cent sulfathiazole ointment proved to be of little value in most of the cases. On small superficial lesions tincture of iodine was effective if used when the lesion first occurred. In the cases in which the lesions were deep and suppurative, the course of treatment which appeared to be most effective was the use of iodides intravenously and by mouth. Usually the patient was given an intravenous injection of 2 Gm. of sodium iodide at the first visit and instructed to take 5 to 15 drops of a saturated solution of sodium iodide three times a day. Injections were repeated at successive visits, and oral therapy continued until the lesions had healed. In several cases, 5 per cent sulfathiazole ointment or

merthiolate ointment 1 to 2,000 was used locally with the iodide therapy, to control any associated bacterial infection. In cases in which the lesions were small and more superficial the injections of iodides as well as the local therapy were omitted, and only the iodides orally were prescribed. The lesions usually showed definite improvement with iodide therapy at the end of the first week. The smaller lesions healed in three to four weeks, but the deeper more extensive lesions took four to six weeks for complete cure. Manual epilation of hairs and draining of the pustules aided the healing process.

The benefit of topical therapy with sulfonamide compound was questionable. In 1 case, however, in which a coexisting bacterial infection due to *S. hemolyticus* was present, the use of sulfathiazole orally and locally cleared the bacterial infection and dealt as satisfactorily with the fungous infection as did the iodides.

#### EVIDENCE FOR THE ANIMAL ORIGIN OF THE INFECTIONS

That human infection with the faviform trichophyta are always either directly or indirectly of animal origin has become evident from the literature. The majority of cases reported have occurred among farm workers, especially workers concerned with the care of cattle.<sup>12</sup> There is also evidence that faviform trichophyton infections have been contracted from horses,<sup>13</sup> from a donkey,<sup>10</sup> from sheep<sup>4</sup> and from a goat.<sup>14</sup>

In this series of 23 cases of suppurative ringworm, 16 of the patients were men, all of whom were farmers who cared for cattle. One woman lived on a farm and did milking. The 5 children in this series all lived on farms. Three of these children had apparently contracted the infection secondarily from older members of the family who had active lesions. In all but 1 instance, in which the patient had not been questioned, patients with primary infections due to the faviform trichophyta gave a definite history of contact with cattle bearing typical ringworm lesions. This was confirmed in several instances by the local veterinarians who were treating the cattle for ringworm. In 1 case hairs obtained from the infected cattle presented the typical large-spored ectothrix parasitism seen in infections due to the faviform trichophyta. *T. discoides* was isolated from hairs obtained from other cattle.

12. Ashton, G.: Cattle Ringworm in Man, *Lancet* **1**:97-99, 1932. Milochevitch, S.: *Trichophyton immersens et ses manifestations cliniques*, *Mycopathologia* **1**:88-97, 1938. Kister, J., and Delbanco, E.: Zur Kasuistik der Kälberflechte, *Arch. f. Dermat. u. Syph.* **130**:484-486, 1921.

13. Hagan.<sup>2</sup> Mackinnon.<sup>7</sup> Sabouraud.<sup>10</sup>

14. Catanei, A., and Izac, R.: Nouvelle teigne d'origine animale observée chez un indigène algérien, *Arch. Inst. Pasteur d'Algérie* **19**:339-341, 1941.

It is important to note that *T. mentagrophytes* was isolated in 4 instances from patients with deep suppurative lesions. The patients also were farmers and had contact with cattle, but in none of the cases had the patients observed ringworm on their cattle. The source of the infection with *T. mentagrophytes* is therefore unknown, but because the patients presented suppurative lesions grossly identical with the lesions caused by the faviform trichophyta it seemed important to include them in this series. It seems highly probable that these infections were also cattle borne, as reports in the veterinary literature indicate that *T. mentagrophytes* is a common cause of ringworm in cattle and may be transmitted to man.<sup>2</sup>

The gross lesions in cattle caused by the faviform trichophyta are similar to lesions produced by any of this genus of fungi. They occur chiefly on the head and neck and in the anal region. They are typically flat, raised, grayish white, well defined plaques, from which broken hairs protrude. If the crusts are pulled off, a moist bleeding surface will be exposed. Pus may accumulate beneath the crusts. After one to two months the crusts come off and leave a bald patch, in which desquamation occurs for a time. This subsequently heals, and the area becomes covered with hair. In calves the lesions usually occur about the mouth and have a thick branlike appearance. The faviform trichophyta will produce pure endothrix as well as ectothrix parasitism of the hair of cattle. It has been observed that in calves frequently only the endothrix parasitism occurs.<sup>15</sup>

#### EXAMINATION AND CULTURAL STUDIES OF CLINICAL MATERIAL

Examination of hairs, scales and pus was made in all cases presented in this series. In infections due to *T. mentagrophytes* parasitized hairs were readily demonstrated. However, in infections due to the faviform organisms examination of a large number of hairs was usually required before evidence of parasitism could be observed. In both types of infection the spores are arranged in chains, forming a sheath on the outside of the hair, and mycelial threads can be seen in the interior of the hair itself (fig. 4). The spores of the faviform trichophyta are larger than those of the gypsum group of trichophyta, but the size of the spores is difficult to ascertain in routine examination of parasitized hairs. Culture of the hairs is necessary to determine the causative organism.

Examination of the scrapings from the skin did not reveal mycelial elements in all cases, and cultures from this material were negative for fungi.

15. Carol, W. L. L.: A Case of Infection with *Trichophyton Faviforme Album*, and a Case of Infection with *Microsporion Orientale* (New Species), *Urol. & Cutan. Rev.* 32:19-23, 1928. Baudet, E. A. R. F.: Particularités d'une teigne megasporée d'un veau, *Ann. de parasitol.* 8:520-522, 1930.

In well developed lesions gram-stained smears of the pus showed large gram-positive spores, which occurred singly and in short chains. The presence of spores in the pus greatly facilitated the attainment of pure cultures.

In 4 cases, *T. mentagrophytes* was isolated on Sabouraud's maltose agar ("difco"). Typical white, powdery to fluffy colonies, with all the structures typical of the trichophyton group, appeared within ten days. In many cases, however, in which material from the deep suppurative lesions was used as an inoculum, the Sabouraud maltose agar remained sterile. In most instances it was observed that the blood agar plates (prepared with blood agar base ["difco"], 5 per cent citrated human blood), which were also used routinely in all cultures from suppurative lesions, supported the growth of a fungus which would not grow, even when transplanted, on the maltose agar. These fungi, which could be isolated on the blood agar base (the addition of the blood to this medium was of no advantage) and which could not be isolated or grown on the maltose agar, were later identified as the faviform trichophyta, *T. album* and *T. discoides*.

Investigations of the requirements for growth of *T. discoides* by Robbins, Mackinnon and Ma<sup>16</sup> have shown that this organism suffers from complete deficiencies for pyridoxine, inactive inositol and molecular thiamine and partial deficiencies for unidentified substances present in peptone, casein hydrolyzate, hydrolyzed egg albumin, malt extract, gelatin and filtrate (DR fraction) from white potatoes. The authors demonstrated that vigorous growth could be obtained on a thiamine and peptone medium.

Our successful isolation of the faviform trichophyta (*T. album* and *T. discoides*) on blood agar base indicated that this medium supplied the necessary factors for growth which were absent in Sabouraud's maltose agar. Blood agar base successfully supported the typical glabrous vegetative growth of the faviform trichophytons, producing colonies which resembled clearly the colonies described by Sabouraud on his classic proof mediums. (The original classic proof mediums of Sabouraud undoubtedly contained many growth substances which are absent in the more purified products used in the artificial mediums now commercially available.) On Sabouraud's proof medium, which we were able to reproduce, and on the blood agar base, *T. album* typically produces a glabrous spongy heaped-up vermicular colony of the color of wax. This may become dark tan to brown after several weeks, and some white powdery growth may appear at the base of the acuminate colony (fig. 5A). *T. discoides* produces on these mediums a colony

16. Robbins, W. J.; Mackinnon, J. E., and Ma, R.: Vitamin Deficiencies of Trichophyton discoides, Bull. Torrey Club 69:509-521, 1942.

which is also habitually glabrous, but has a fairly regular disk shape and a small raised center which may or may not be present. The colony frequently has a grayish tan to grayish yellow pigment and has a powdery or velvety surface of short fine white down (fig. 5B). Microscopic examination of these glabrous colonies reveals irregular mycelia with an abundance of irregularly formed intercalary and terminal chlamydospores. The appearance is similar to the "favic chandeliers" seen in

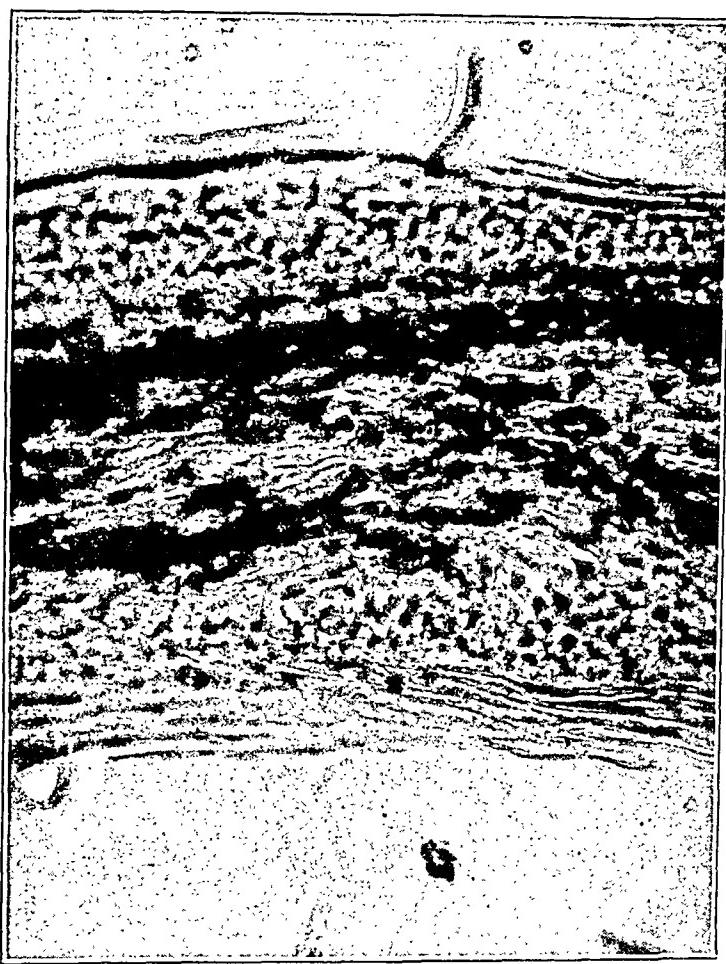


Fig. 4.—Typical hair, showing ectothrix parasitism by *T. album*.

the causative organism of favus. Spore-bearing structures are characteristically absent.

The addition of thiamine to the blood agar base, 0.1 mg. per hundred cubic centimeters, improves this medium for purposes of isolation. On the medium enriched with thiamine, growth may appear in some instances five days after inoculation, and vigorous colonies are produced with white fluffy surface growth (fig. 5 [C and D]). The colonies show all the structures (microconidia and macroconidia) which are characteristic

of the trichophyton group (fig. 6). After growth on the enriched medium, transplants may be made to a medium with less thiamine content, such as plain blood agar base ("difco") or Sabouraud's maltose agar ("difco"), on which the typical glabrous characteristics of the colonies, used in identification of the various species, are more apparent.

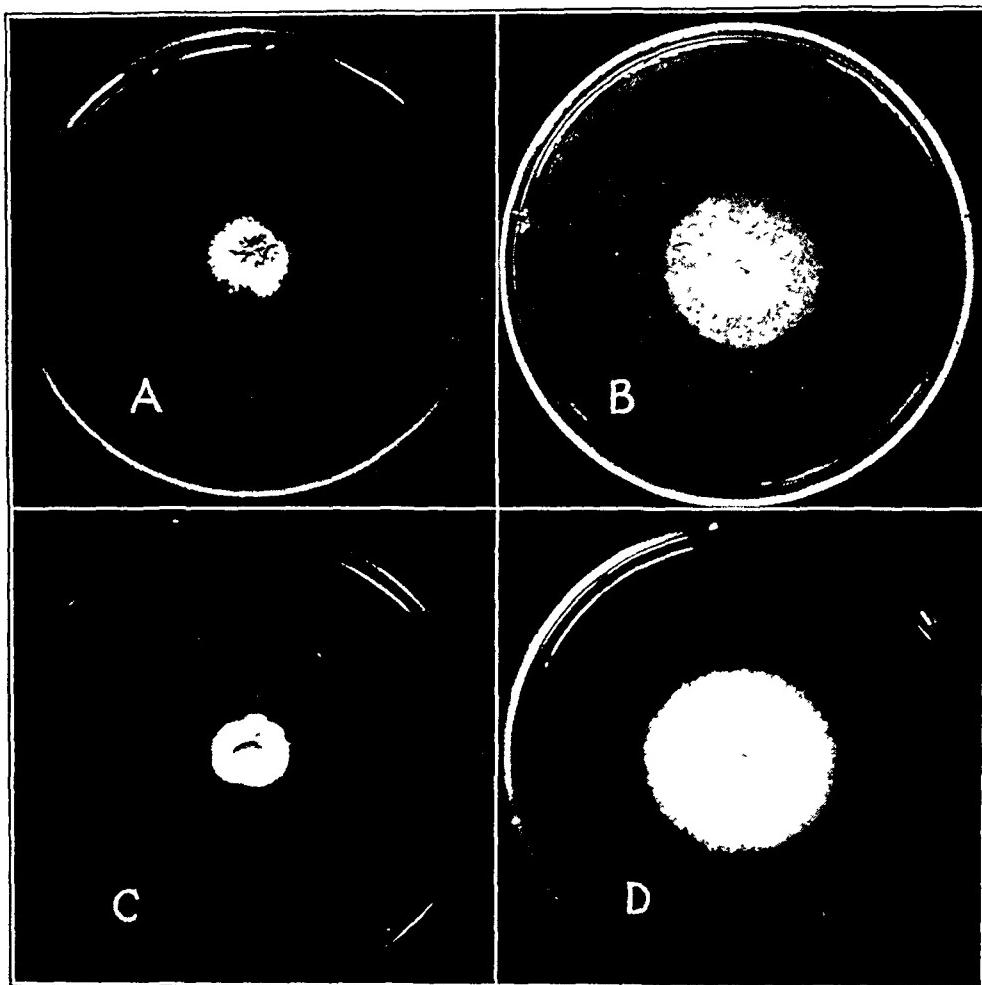


Fig. 5.—Trichophyton cultures on blood agar base ("difco") in forty-two days. *A*, *T. album*. *B*, *T. discoides*. *C*, *T. album* (blood agar base plus thiamine [0.1 mg. per hundred cubic centimeters]). *D*, *T. discoides* (blood agar base plus thiamine [0.1 mg. per hundred cubic centimeters]).

Further studies on the cultural characteristics and requirements for growth of the organisms isolated in this series of cases are presented in a second paper.<sup>17</sup>

Inoculations with *T. album* and *T. discoides* obtained from the patients were unsuccessful in guinea pigs, but produced typical ringworm

17. Georg, L.: Growth Characteristics of the Faviform Trichophytons, to be published.



Fig. 6.—Microconidia and macroconidia formed on a blood agar base ("disco") enriched with thiamine. *T. discoides*.



Fig. 7.—Lesion produced in rabbit twenty days after inoculation with *T. album* isolated from a patient in this series.

lesions in rabbits (fig. 7). The hairs showed ectothrix parasitism, and the scales were filled with chains of arthrospores. Pure cultures of *T. album* and *T. discoides* were obtained from the lesions in the rabbits.

#### SUMMARY

Twenty-three cases of deep suppurative ringworm infections contracted from cattle are reported. Descriptions of the lesions, their clinical course and the treatment used are given in detail. Examination of clinical material and cultural studies showed that in 14 cases the infection was caused by faviform trichophyta, in 12 cases by *Trichophyton discoides* and in 2 cases by *Trichophyton album*. Cultures in 4 cases yielded one of the gypseum trichophyta. *Trichophyton mentagrophytes*. In the remaining 5 cases in this series, pathogenic fungi were not observed on hairs, nor could they be grown in cultures. However, the nature of the lesions, the absence of bacterial infection and the history of contact with cattle infected with ringworm indicate that these cases were also of ringworm contracted from cattle. Blood agar base ("difco") enriched with thiamine is suggested as an isolation medium for use in cases of deep suppurative ringworm in which infection with the faviform trichophyta is suspected. Typical ringworm lesions were obtained in rabbits from inoculations with cultures of *T. album* and *T. discoides* from patients in this series, and pure cultures of the organisms were recovered.

Dr. Rhoda W. Benham of the Department of Dermatology, College of Physicians and Surgeons of Columbia University, gave guidance in the mycologic work.

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## ACQUIRED LOOSE SKIN (CHALAZODERMA)

Report of a Case

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ABNORMALITIES in the distensibility and elasticity of the skin have been described for centuries under a variety of names. Considerable confusion has arisen in the nomenclature concerning diseases reported under such terms as cutis laxa, dermatolysis, cutis hyperelastica, cutis pendula, loose skin, dermatochalasis, pachydermatocele, chalazoderma, chalodermie, cutaneous geromorphism, dermatomegaly, lax skin, Ehlers-Danlos syndrome, elephantiasis and many others. These terms are loosely applied and tend to overlap in meaning.

In general, the aforenamed diseases can be separated fairly well into several groups:

1. Dermatolysis is the term first used by Alibert<sup>1</sup> in 1835 to describe hypertrophic disorders of the skin associated with laxness but without hyperelasticity. There seem to be two types (which may be related): first, generalized diffuse hypertrophy of the skin which hangs in heavy folds and is coarse and usually rough and, second, localized neurofibromatosis (von Recklinghausen's disease). Either may be congenital and may be associated with cutis verticis gyrata or similar diseases of the scalp. Alibert classified the disease into six subdivisions, dependent on the area affected. Sequeira,<sup>2</sup> Wise and Snyder,<sup>3</sup> Bielschowsky,<sup>4</sup> Rossi,<sup>5</sup> Umar,<sup>6</sup> Creite,<sup>7</sup> Vaglio<sup>8</sup> and Wigley<sup>9</sup> discussed cases belonging

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1. Darier, J.: *Précis de dermatologie*, ed. 4, Paris, Masson & Cie, 1928.
2. Sequeira, J. H.: *Cutis pendula*, Proc. Roy. Soc. Med. **9**:84, 1916.
3. Wise, F., and Snyder, E. J.: Diffuse and Disseminate Dermatolysis: Report of a Case, J. Cutan. Dis. **32**:139, 1914.
4. Bielschowsky, F.: Clinical Symptoms and Pathology of Circumscribed Lipatrophy (*Cutis Laxa*), Deutsches Arch. f. klin. Med. **166**:96, 1930.
5. Rossi, G.: On a Case of Concetti's Dermatomegaly (*Cutis Laxa*), Riv. di clin. pediat. **26**:137 (Feb. 25) 1928.
6. Umar, M.: A Case of Dermatolysis, Indian M. Gaz. **62**:208 (April) 1927.
7. Creite, O.: Zwei seltene Fälle von Missbildungen: I. Wampenbildung an Kopf, Hals, und Brust; II. Doppelseitige erbliche Quadratfüsse, Deutsche Ztschr. f. Chir. **197**:251, 1926.

(Footnotes continued on next page)

to this group. Sainz and Bravo<sup>10</sup> stated that these cases rightly belong in the group of nevoid disorders.

2. There are also described<sup>11</sup> other congenital cases which begin with generalized edema at birth, the edema being followed by diffuse dermatolysis. A biopsy in the case described by Raspi showed hypogenesis of the elastic tissue, laxness of the connective tissue bundles and a notable increase in the lymphatic network. Endocrine disturbances were postulated in these cases.

3. Cutis hyperelastica is the disease which van Meek'ren first described in 1682, and it has since been reported by many writers<sup>12</sup> under various terms. Frequently the extremely elastic skin is associated with hyperextensibility of the joints, deformities of the bones and a susceptibility of the skin to trauma; this group of dystrophies comprises the Ehlers-Danlos syndrome. Persons with this syndrome are the "india rubber men" of the circus. The syndrome seems to be inherited. Debré and his associates<sup>13</sup> reported a similar case, with osseous changes and hyperextensible joints and with looseness but relative inelasticity of the skin.

4. There is an acquired cutaneous disease, or group of diseases, in which local or generalized atrophy, laxness and inelasticity of the skin follow an inflammatory process. Sutton,<sup>14</sup> Fuhs<sup>15</sup> and Goodman and Traub<sup>16</sup> reported examples of the localized form, and in 1891 Souques

8. Vaglio, R.: Un caso di cutis laxa, *Pediatria* **31**:321 (March 15) 1923.

9. Wigley, J. E. M.: Dermatolysis (Cutis Laxa), *Proc. Roy. Soc. Med.* **36**:294 (April) 1943.

10. Sainz de Aja, E. A., and Bravo, J.: Unna-Jadassohn's Cutis Verticis Gyrata Compared with Alibert's Dermatolysis, *Arch. Dermat. & Syph.* **8**:797 (Dec.) 1923.

11. Negri, F.: A Case of "Cutis Laxa," *Pediatria d. med. prat.* **9**:106 (Feb.) 1934. Raspi, M.: On a Case of Cutis Laxa, *Riv. di clin. pediat.* **25**:648 (Sept.) 1927.

12. Comby, J.: Cutis laxa et syndrome d'Ehlers-Danlos, *Arch. de méd. d. enf.* **40**:107 (Feb.) 1937. Berggreen, P.: Zur Kenntnis der Erblichkeit der Cutis laxa (Gummihaut), *Dermat. Wchnschr.* **104**:374 (March 20) 1937. Benjamin, B., and Weiner, H.: Syndrome of Cutaneous Fragility and Hyperelasticity and Articular Hyperlaxity, *Am. J. Dis. Child.* **65**:247 (Feb.) 1943. Capurro, R.: Lax Skin, Hematoma, Cutaneous Atrophies, Muscular Hypotonia and Articular Laxity, *Arch. latino-am. de pediat.* **20**:713 (Nov.) 1926. Kalz, F.: Cutis laxa als Symptom allgemeiner Stützgewebswäche, *Arch. f. Dermat. u. Syph.* **171**:155, 1935.

13. Debré, R.; Marie, J., and Seringe, P.: "Cutis laxa" avec dystrophies osseuses, *Bull. et mém. Soc. méd. d. hôp. de Paris* **53**:1038 (July 12) 1937.

14. Sutton, R.: Diseases of the Skin, ed. 8, St. Louis, C. V. Mosby Company, 1931.

15. Fuhs, H.: Ueber Dermatochalasis, *Wien. klin. Wchnschr.* **39**:1331 (Nov. 11) 1926.

16. Goodman, H., and Traub, E. F.: Dermatolysis, *Surg., Gynec. & Obst.* **42**:88 (Jan.) 1926.

and Charcot<sup>17</sup> described fully a remarkable case of generalized lax skin, cutaneous geromorphism, occurring in a girl of 11 within two months after an unusual systemic illness, characterized by fever, headache and abdominal pain followed by recurring papular eruptions "like mosquito bites." The skin became soft, loose and inelastic and hung in folds, especially at the neck, abdomen and about the roots of the extremities, giving her the appearance of extreme old age.

5. Chalazoderma is the classification into which the case herein reported falls. It differs from the last particularly by the absence of prodromal disease, inflammation or edema. In these cases the loose inelastic sagging skin is soft and thin, yet without superficial atrophic changes of old age. It occurs in young to middle-aged adults. Von Kétyl<sup>18</sup> in 1901, under the name "chaloderminie," reported a case of severe disease in a 30 year old woman who visited the clinic for a disorder of the respiratory tract. The cutaneous changes began at the age of 18, with sudden onset, and did not progress after a few months. The gluteal regions were most severely involved, and the skin in this area was likened to the "formless, ill-fitting, wide breeches of a Bosnian soldier." The breasts, which had been firm, hung lax and wide. Likewise, the skin of the abdomen and back was soft and loose and hung in pliable folds. In this case the face and neck were not involved, and over the back the thin skin allowed the bluish red vessels to show through. The patient showed no wasting of the muscles and no change in the skeletal structure and was in good health except for the infection of the respiratory tract, which healed in about two months. Weber<sup>19</sup> and Petges and Lecoullant,<sup>20</sup> in mentioning this case, stated that it was a hypertrophic disease related to neurofibromatosis (von Recklinghausen's disease). The photographs tend to suggest this, but the clinical description and the report of biopsy force one to consider the disease as one of those with destruction of the cutaneous supportive tissues. According to von Kétyl the epidermis and upper part of the dermis were normal except for slightly increased pigment in the basal layer. The changes were limited to the deeper pars reticularis and the subcutis and consisted of edema with dilatation and thrombosis of the vessels, infiltration of young connective tissue cells and a decrease in number of collagenous and elastic bundles and with shredding and twisting of

17. Souques, A., and Charcot, J. B.: Géromorphism cutané, Nouv. Iconog. d. Salpêtrière **4**:169, 1891.

18. von Kétyl, L.: Ein Fall von eigenartiger Hautveränderung: "Chalodermie" (Schlaffhaut), Arch. f. Dermat. u. Syph. **56**:107, 1901.

19. Weber, F. P.: Chalasodermia or "Loose Skin" and Its Relationship to Subcutaneous Fibrous or Calcareous Nodules, etc., Urol. & Cutan. Rev. **27**:407 (July) 1923.

20. Cited by Darier, J., and others: Nouvelle pratique dermatologique, Paris, Masson & Cie, 1936.

the collagenous fibers and granular degeneration and clumping of the elastic material.

In 1937 Goth<sup>21</sup> described a similar example, although of less severe disease, under the same name. His case occurred in a 23 year old woman who had been well until the age of 13, when she began to lose weight and dropped from 60 to 51 Kg. No explanation had been found, and she continued to be otherwise well until, at the age of 19, she suffered an attack of polyarthritis, beginning in the feet and spreading to the other joints. It apparently subsided without sequelae, but some time after this the skin changed, on the face becoming soft, pale and slightly brown and showing telangiectases, but no drooping or folding. On the arms and upper part of the thighs and over the scapulas and buttocks the skin was soft, pale, lax, thin and folded. Biopsy showed no change other than a paucity of elastic fibers, those remaining being frayed, disordered and clumped. No infiltrate was present. Goth points out that in these 2 cases there was no inflammation or edema of the skin prior to the onset of the disease and that although in 1 case there was a vascular element on the back and in the other on the face it was of different character than that seen in acrodermatitis atrophicans chronica. Ormsby and Montgomery<sup>22</sup> and Jadassohn<sup>23</sup> made cursory mention of cases of disease which may approximate the cases described as "chalodermie." Mraček,<sup>24</sup> in discussing blepharochalasis, described the same histologic changes demonstrated in our patient.

Also confusing the picture to a slight extent are the various forms of elephantiasis due to lymphangiomas and to chronic lymph stasis, as in Milroy's disease, elephantiasis nostras and filariasis.

Aside from Alibert's dermatolysis and cutis hyperelastica the literature is only sparsely provided with examples of these diseases, and many of those which do appear either are reported without photographs, biopsies or adequate descriptions or were reported many years ago, with the result that accurate delineation among them is impossible. Moreover, when there were prodromal signs or symptoms, they usually were not observed by the person reporting the case and cannot be evaluated.

#### REPORT OF A CASE

B. E. was first seen at the University Hospitals in September 1932, because of pelvic relaxation, and was admitted to the hospital for gynecologic surgical treatment. Her difficulty began in 1904 with the birth of her first child, and in 1907 a repair of further laceration suffered during her second delivery was

21. Goth, A.: Ueber Chalodermie (Kéty), Dermat. Wchnschr. **104**:426 (April 3), 1937.

22. Ormsby, O. S., and Montgomery, H.: Diseases of the Skin, ed. 6, Philadelphia, Lea & Febiger, 1943.

23. Jadassohn, J.: Dermatologie, ed. 2, Vienna, Weidmann & Company, 1938.

24. Mraček, F.: Handbuch der Hautkrankheiten, Vienna, Alfred Hölder, 1902.

necessary. A third delivery in 1916 broke down this repair, and increasing symptoms of pelvic pressure and backache ensued. Prolapse of the cervix through the vaginal orifice was noted in 1925. The general health had always been good. On physical examination a relaxed abdomen was noted, with many striae distensae; the uterus was poorly supported and there was an egg-sized cystocele, as well as a uterine fibroid, chronic cervicitis and cervical lacerations. The perineal support was good. No sign of the subsequent cutaneous deformity was observed. A vaginal hysterectomy and perineorrhaphy were performed, and the patient returned home after a convalescence prolonged by pelvic inflammation and pleuritis.

In December 1936 the patient returned to the hospital for admission to the department of ophthalmology, because of drooping of the eyelids. She stated that this had begun eighteen months previously and had been progressive to the point of obscuring her vision. The resulting entropion of the upper lids caused chronic conjunctivitis. There was mild ectropion of the lower lids. She denied any inflammation of the lids prior to or during these changes. The skin was soft and loose and gave the impression that the subcutaneous structures were gone. The redundant skin was resected from both eyelids, with a satisfactory result. The conjunctivitis improved, and the patient was discharged with a diagnosis of blepharochalasis. It is unfortunate that no sections were made from the resected skin. The skin was still normal elsewhere.

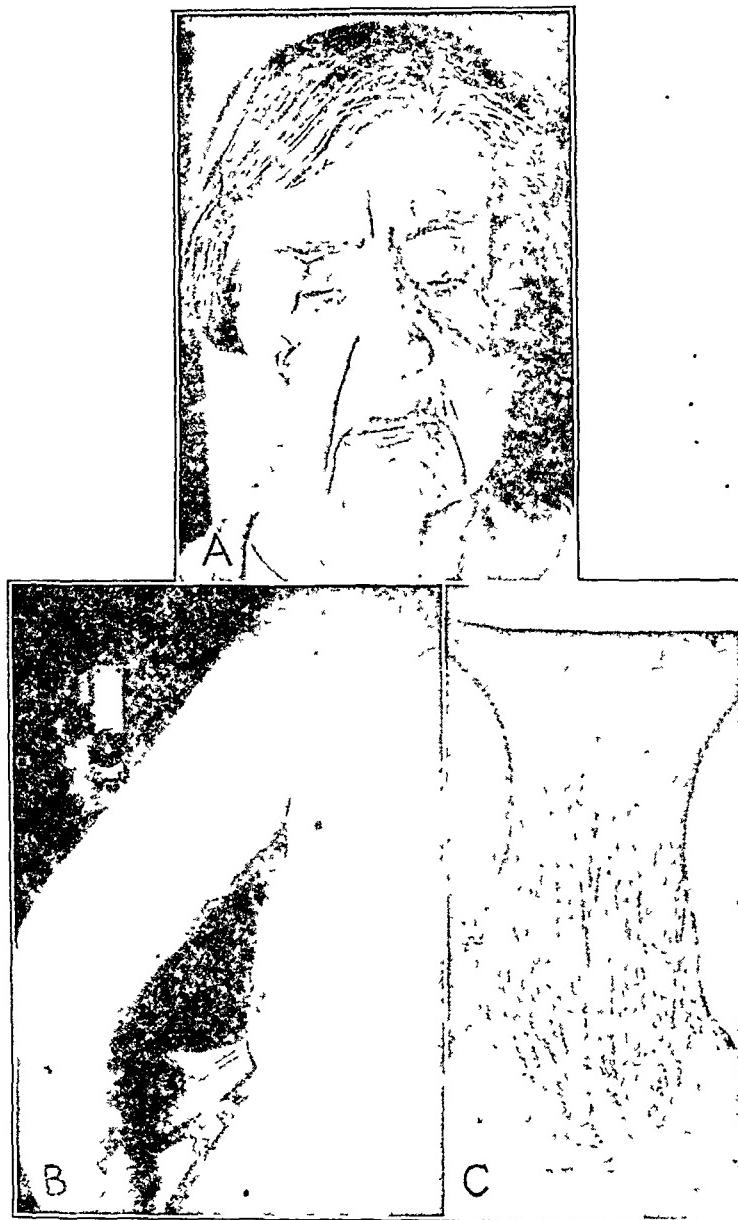
In February 1937 she was readmitted, this time to the department of otolaryngology for treatment of chronic otitis media on the left side, which healed with conservative treatment. The blepharochalasis had progressed to some extent since the operation, but was satisfactorily controlled with the use of "scotch tape" to support the lids. There were still no changes in the skin other than that of the eyelids.

The patient was not seen again in this hospital until April 1942, when she returned to the department of obstetrics and gynecology for treatment for backache and cystocele. For the first time she showed the widely distributed changes in the supportive structures of the skin and was referred to the department of dermatology and syphilology for study. The patient stated that the cutaneous changes had been gradual and could not guess when the relaxation began to be evident in areas other than the lids, but it was presumably in 1937 or 1938.

Her general appearance was one of weakness and fatigue. The eyelids were supported by means of cellulose adhesive tape, but there was still entropion of the upper lids and ectropion of the lower ones. The forehead was deeply furrowed. The cheeks drooped, and the skin of the neck hung loosely, like a dewlap (fig., A). On the inner surface of the arms and on the contiguous part of the thorax the skin was also loose and folded (fig., B). Likewise, over the scapulas there were many soft thin folds. The breasts were lax and flaccid; the abdominal skin was flabby, and the skin of the buttocks, vulva and upper part of the thighs was loose and folded. The skin in all of the affected areas was fine, soft, inelastic and pale, without telangiectases, keratoses or other senile changes. The vaginal introitus was relaxed. Opinion of the gynecologists differed in respect to whether the pelvic relaxation was of the same nature as was usually seen, but a large cystocele and partial prolapse of the vault were noted. The general physical examination revealed no abnormalities except for moderate cardiac enlargement and blood pressure of 215 systolic and 100 diastolic. Neurologic examination revealed no sign of neurologic or muscular dystrophy. The patient was somewhat weaker than would be expected in a 57 year old woman. Quinine increased her weakness slightly, and neostigmine compound relieved it, but in the opinion of the consulting neurologist this was of no significance in respect to a diagnosis of myasthenia gravis, which had been suggested. The Wassermann reaction

of the blood was anticomplementary, but the reactions in Kahn and Kline tests were negative, these serologic observations being constant throughout her previous visits. The blood cell count and urinalysis revealed no abnormalities. A specimen for biopsy was taken from the skin of the right cheek. After an uneventful convalescence following anterior colporrhaphy and perineorrhaphy the patient returned home.

Microscopic examination of the biopsy section revealed thinning of the epidermis, with loss of the papillae. The hair and the sebaceous and sudoriferous



A, relaxation and drooping of the skin of the eyelids, cheeks and neck. The site of biopsy is visible on the right cheek. "Scotch tape" supports the right eyelid. B, drooping and formation of fine folds of skin on the posterior and lateral aspects of the thorax and inner surface of the arm. C, relaxation, sagging and folding of the skin of the vulva.

glands were normal. The tissues of the dermis appeared fragmented. Sections stained by Weigert's method showed loss of the elastic tissue in the pars papillaris, with advanced changes of the collagen to collastin. There was no normal elastic

tissue in the pars reticularis, the fibers being short and shredded and taking little stain. (It was impossible to be certain whether any of this was elastic tissue or whether it represented only degenerated collagenous tissue.) There was no disturbance of the elastic tissue in the sweat glands and vessels, and the subcutaneous fat was apparently normal.

In September 1942 the patient was called back to the hospital for further study. No noticeable change or progression had occurred in the cutaneous disease, and her other complaints had lessened. The physical examination revealed nothing new. Roentgenologic studies of the skull revealed no enlargement of the sella turcica and no other abnormalities. The basal metabolic rate was —10 per cent. Plastic procedures on the face were being considered, when pharyngitis developed and cultures of material from the throat grew virulent Klebs-Loeffler bacilli. She was transferred to the isolation wards, where the pharyngitis cleared quickly and without consequence, but the cultures remained positive. Thorough attempts to end her carrier status failed, and after five weeks' she was returned home at her own request, in the custody of her county health officer. The patient has not returned to the hospital since that time.

This patient thus presents dystrophy of the connective tissues of the skin, probably associated with a similar disease of the pelvic supportive structures, progressive over a period of at least eight years, with abnormal looseness, inelasticity, drooping and folding of the skin of the eyelids, face, neck, thorax, abdomen, external genitals, arms and upper part of the thighs. The case fits well into the fifth group described, chalazoderma, and agrees in most respects, both clinically and microscopically, with the cases reported by von Kétyl and Goth. Our patient, in contradistinction to theirs, showed the most decided changes about the face and neck and presented no telangiectases or other senile changes. Like theirs, there was no prodromal inflammation or edema and no hypertrophy either diffuse or in localized tumor masses.

#### SUMMARY

The literature on abnormalities in the distensibility of the skin is reviewed, and the types are classified into five groups on a basis of clinical and microscopic differences.

An unusual case of chalazoderma, fitting into the fifth group, is described.

## ALLERGIC CONTACT DERMATITIS DUE TO WOOL FAT AND CHOLESTEROL

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THE PURPOSE of this report is to record 9 cases of contact dermatitis due to an oxycholesterol-petrolatum ointment base ("aquaphor") and related substances. Many cosmetic preparations contain wool fat and cholesterol, the active ingredient of wool fat. The sensitizing qualities of wool and wool fat are well known, but despite the widespread use of wool fat in many ointment bases and cosmetic creams there are few reports of dermatitis due to its use. The term allergic contact dermatitis is used in the title to differentiate this type of dermatitis from nonallergic contact dermatitis due to primary chemical or mechanical irritants.

In order to have the proper perspective, one should note that this article was written early in 1942, when sulfathiazole ointment had become popular and many articles were being published extolling its value. Only a few authors were reporting cases of contact dermatitis due to this drug, but soon severe allergic contact dermatitis due to local use of sulfathiazole was observed so frequently that the local use of this drug was condemned by many dermatologic societies.

### REPORT OF CASES

CASE 1.—H. P., a white man aged 45, was first seen in October 1941, because of acute dermatitis of two days' duration on the face, neck, upper part of the chest and shoulders. The eruption consisted of confluent erythematous edematous dermatitis. The borders were made up of slightly infiltrated, erythematous plaques, varying in diameter from 1 to 3 cm. On the ankle there was a well defined, 4 by 8 cm., infiltrated and crusted plaque of one month's duration. It was surrounded by an ill defined zone of acute dermatitis of more recent origin. Compresses of diluted solution of aluminum acetate and phenol 0.4 cc., solution of aluminum acetate 6 cc., and "aquaphor" in sufficient quantity to make 60 Gm. were prescribed. After five days of this treatment the eruption was worse. Patch tests were made with the ointment containing "aquaphor," the pure (?) crystalline cholesterol (Boekringer & Son), the cholesterol supplied by the manufacturers of "aquaphor" (Duke Laboratories), "nivea creme," "tecto," anhydrous wool fat, the absorption base (Johns Hopkins Dispensary) and shaving cream (Parke, Davis & Company). Positive reactions were elicited to all of the substances. Patch tests with liquid petrolatum, olive oil, petrolatum, "qualatum" (Almay Pharmaceutical Corporation), several types of soaps and raw untreated wool, taken

directly from a sheep, elicited negative reactions. The patient had used 5 per cent sulfathiazole in "aquaphor" for chronic dermatitis on the ankle. The ointment caused acute dermatitis of the face and neck. In view of the tests the ointments containing "aquaphor" or wool fat were discontinued, and the eruption underwent involution in approximately one month.

Three years later the patient was retested with pure cholesterol, and a reaction of 3 plus was elicited.

CASE 2.—E. F., a white man aged 31, was first seen in October 1941. He complained of a chronic pruritic lichenoid eruption on the shins. It consisted of moderately well defined, dull red, conical papules with numerous excoriations and follicular pustules. He was treated with small doses of unfiltered roentgen rays, and 5 per cent sulfathiazole in "aquaphor" was prescribed. Five weeks later acute dermatitis was superimposed on the original eruption. Patch tests with the prescribed ointment gave a reaction of 3 plus. There were similar reactions to tests with cholesterol (Duke Laboratories), an absorption base (Johns Hopkins Dispensary formula) and anhydrous wool fat. Tests with "nivea creme" and "qualatum" produced weaker reactions. He was not sensitive to petrolatum. On November 27 his dermatitis was complicated by generalized

TABLE 1.—*Constituents of "Aquaphor" and Related Preparations*

Preparation	Alcohols and Esters of Cholesterol	Aliphatic Hydro- carbons	Water	Glycerin	Miscellaneous
"Aquaphor".....	+	+			
"Tecto".....	+	+	+	+	
"Nivea creme".....	+	+	+	+	
"Nivea skin oil".....	+	+	+	+	Perfume Perfume; sodium borate

furuncles. Sulfathiazole, 1 Gm. four times a day, was prescribed. On the following day a generalized morbilliform eruption developed. Use of the drug was then discontinued.

CASE 3.—L. C., a white woman aged 39, in January 1942 presented an eruption of one month's duration. It started in the retroauricular regions and then involved the face, neck, chest, back, axillas and scalp. The dermatitis was erythematous vesicular and crusted. Patch tests showed that she was sensitive to nickel, 2.5 per cent sulfathiazole in "aquaphor," "tecto," "aquaphor," "nivea skin oil," cholesterol (Duke Laboratories), pure (?) cholesterol crystals and "Frederick's shampoo." Reactions were negative to tests with "pine oil soapless shampoo," "Vernon wave set," "qualatum" and a small piece of a woolen dress which she had worn at the time of the onset of the eruption. The patient had previously used the two shampoos, the wave set and the 2.5 per cent sulfathiazole ointment. The dermatitis was apparently due to the "Frederick shampoo" and was aggravated by the use of "aquaphor" containing sulfathiazole.

CASE 4.—E. H., a white woman aged 48, when first seen in January 1942 had had for three weeks an acute, weeping dermatitis on the face, neck, upper part of the chest, arms and hand. On other parts of the body the eruption consisted of discrete and confluent, erythematous, slightly scaly macules. The eruption disappeared after the use of compresses of solution of aluminum acetate and an emulsion of bentonite, water and olive oil. Reaction to patch tests with Barbara Gould "velvet of roses face cream" were strongly positive, and the reactions

to other tests with wool fat, "curex cream" and "Hind's deodorant" (containing aluminum sulfate) were negative. Approximately one month later an ointment containing "aquaphor" was prescribed. Within twenty-four hours after this salve was applied severe acute dermatitis developed on her face, neck and shoulders and on both surfaces of her forearms. Reactions to patch tests showed that she was sensitive to the "aquaphor" ointment, wool fat and cholesterol (Duke Laboratories), but not to "qualatum." The patient gave a history of previous ingestion of sulfathiazole, which had resulted in an eruption and fever.

CASE 5.—J. M., a white man aged 41, presented in September 1941 moderately active dermatophytosis of the feet. Equal parts of "aquaphor" and zinc oxide ointment were prescribed. He was not seen again for six weeks. When he returned there was extensive acute vesicular dermatitis of the feet and legs. Reactions to patch tests with the prescribed ointment, "nivea creme," "tecto," anhydrous wool fat, absorption base (Johns Hopkins Dispensary), cholesterol (Duke Laboratories) and "aquaphor" were positive. Reactions to tests with "qualatum," liquid petrolatum and petrolatum were negative. He was given an ointment with "qualatum" as the vehicle. The dermatitis rapidly underwent involution, but relapsed. One month later the reaction to a patch test to "qualatum" was positive. The patient apparently had become sensitive to bases containing wool fat or its active principles, and later sensitivity to "qualatum" also developed.

CASE 6.—R. B., a white man aged 42, was first seen in 1933, complaining of chronic relapsing dermatitis on the left leg. For several years he had applied many ointments containing a wool fat or "aquaphor" base. In the fall of 1941 acute dermatitis developed in the treated area. He gave positive reactions to patch tests with "aquaphor," cholesterol (Duke Laboratories), "nivea creme" and anhydrous wool fat and negative reactions to tests with petrolatum and "qualatum."

CASE 7.—J. C., a white woman aged 38, in the fall of 1941 had applied to her feet a modified ointment of benzoic and salicylic acid in an "aquaphor" base. After several weeks acute dermatitis developed in the area of application. The reactions to patch tests were as follows: with the ointment 3 plus, "aquaphor" 2 plus, cholesterol (two occasions) 1 plus and anhydrous wool fat negative. Several years previously she had applied to her face a mild sulfur ointment with an "aquaphor" base. This had been discontinued, and when she attempted to use the ointment again acute dermatitis resulted.

CASE 8.—F. E., a white woman aged 33, complained of recurrent dermatitis of her hands. The history indicated that she might be sensitive to nickel, and a patch test with 5 per cent nickel sulfate applied for four hours elicited a strongly positive reaction. A reaction of 3 plus was obtained by patch tests with cholesterol (Duke Laboratories). "Qualatum" caused no reaction.

CASE 9.—M. J., a white woman aged 35, had had for four years cheilitis of undetermined cause on both lips. The lesion had failed to respond to numerous local and general therapeutic measures. The patient remarked that various ointments accentuated the cheilitis. In 1941 patch tests with "aquaphor," "nivea creme" "nivea skin oil" and anhydrous wool fat elicited a reaction of 2 plus and with "qualatum" a reaction of 1 plus. The reactions to repeated tests with cholesterol (Duke Laboratories) and with cholesterol crystals were negative. In April 1944 positive reactions were obtained in patch tests with "aquaphor."

## COMMENT

Ramirez and Eller<sup>1</sup> reported the cases of 2 patients who were sensitive to wool fat. One was also sensitive to crude wool and wool extracts (?). Sulzberger and Morse<sup>2</sup> reported 2 patients who were sensitive to wool fat. One was a wool salesman, and the other patient was a dress designer. Hertslet<sup>3</sup> gave an example of a patient with a generalized eruption which resulted from the frequent handling of raw wool. The patient reacted positively to a patch test with wool fat. Milian and Garnier<sup>4</sup> described lichenoid dermatitis due to sensitivity to wool in a farmer who tended sheep. For three years the dermatitis had persisted on the legs and forearms. In discussing the farmer's case, Sézary wrote of 2 patients who were sensitive to wool fat as shown by patch tests. Sézary and Horowitz<sup>5</sup> stated that the active factor was isocholesterol. Cheilitis caused by lipstick was reported by Sézary,

TABLE 2.—Reactions to Patch Tests

Substances Used in Tests	Case Number								
	1	2	3	4	5	6	7	8	9
Ointment with "aquaphor" base.....	3+	3+	3+	3+	3+	2+	3+	..	..
"Aquaphor".....	3+	2+	3+	..	3+	2+	2+	2+	2+
Cholesterol *.....	3+	3+	3+	3+	3+	3+	1+	2+	—
Cholesterol crystals †.....	3+	..	3+	..	..	..	..	..	..
"Nivea creme".....	3+	3+	..	..	2+	2+	..	..	2+
"Tecto".....	3+	..	2+	..	3	..	..	..	..
Anhydrous wool fat.....	2+	2+	..	3+	3+	2+	—	2+	2+
Absorption base :.....	3+	3+	..	..	2+	..	..	..	..
Petrolatum.....	—	—	..	..	—	—	..	..	..
"Qualatum" §.....	—	1+	—	—	2+	—	..	..	1+

\* Duke Laboratories.

† Bockringer & Sons.

‡ Johns Hopkins Dispensary formula (contains cholesterol).

§ Almay Pharmaceutical Corporation.

Horowitz and Genet.<sup>6</sup> The patient was observed to be sensitive to wool fat and eosin. Fanburg<sup>7</sup> reported dermatitis due to "aquaphor" oint-

1. Ramirez, M. A., and Eller, J. J.: The "Patch" Test in "Contact Dermatitis" (Dermatitis Venenata), *J. Allergy* **1**:489, 1930.
2. Sulzberger, M. B., and Morse, J. L.: Hypersensitivity to Wool Fat: Report of Two Cases, *J. A. M. A.* **96**:2099 (June 20) 1931.
3. Hertslet, L. E.: A Case of Allergic Dermatitis Due to Wool, *South African M. J.* **8**:182, 1934.
4. Milian, G., and Garnier, G.: Dermatose des tondeurs de moutons, *Bull. Soc. franç. de dermat. et syph.* **43**:1473, 1936.
5. Sézary, A., and Horowitz, A.: Intolérance cutanée à la lanoline, *Bull. Soc. franç. de dermat. et syph.* **43**:1544, 1936.
6. Sézary, A.; Horowitz, A., and Genet, H.: Cheilité du rouge (intolérance à l'éosine) chez une malade intolérante à la lanoline, *Bull. Soc. franç. de dermat. et syph.* **43**:1542, 1936.
7. Fanburg, S. J.: Dermatitis Due to Aquaphor: Report of a Case, *Arch. Dermat. & Syph.* **42**:479 (Sept.) 1940.

ment and discovered that the sensitivity was due to the cholesterol in "aquaphor," but the reaction to a patch test with hydrous wool fat, which also contained the cholesterol, was negative. In discussing the case of Fanburg's patient, Beerman stated that he had observed a patient who was known to be sensitive to wool in whom dermatitis appeared after the use of "nivea creme." Lord<sup>8</sup> reported 4 cases of cutaneous sensitization to wool: 2 patients had urticaria and 2 an allergic "eczema." None of the patients were sensitive to wool fat. In discussing industrial dermatitis due to wool fat Schwartz and Tulipan<sup>9</sup> described a dermatitis which started soon after occupational exposure to wool. It was an erythematous papulovesicular eruption on the back of the hands. The workman was extremely sensitive to wool. The eruption would clear if he remained away from work for a few days, but would return when he resumed his occupation. Cranch and his associates<sup>10</sup> were able to sensitize to wool fat 7 students in a group of 98 tested.

In 1938, Sulzberger and Goodman<sup>11</sup> described a case in which hypersensitivity to wool fat had developed and had presented an extremely difficult therapeutic problem. Sensitivity to this allergen was unrecognized for several years, and the chronic eruption on their patient's hands failed to improve until the exposure to topical remedies containing wool fat was stopped. Coca and his colleagues<sup>12</sup> listed wool fat as a sensitizer.

Since this report was written, in 1942, no additional cases of sensitivity to wool fat, "aquaphor" or cholesterol have come to my attention, in spite of the fact that I have occasionally used "aquaphor" or "nivea creme" as a base and frequently have prescribed "nivea skin oil" in the bath for generalized pruritus, bath dermatitis and related conditions. It is to be noted that 2 of the 9 patients who showed positive reactions to wool fat and cholesterol were observed to have retained their sensitivity to these substances when tested several years later. Three patients exhibited 3 plus reactions to "qualatum," but attempts were not made to find the exact sensitizing factor or factors.

The negative reactions to tests with cholesterol in case 9 are difficult to explain. The other 8 patients who were sensitive to "aquaphor"

8. Lord, L. W.: Cutaneous Sensitization to Wool, *Arch. Dermat. & Syph.* **26**:707 (Oct.) 1932.

9. Schwartz, L., and Tulipan, L.: *Occupation Diseases of the Skin*, Philadelphia, Lea & Febiger, 1939, p. 707.

10. Cranch, A. G.; Smyth, H. F., and Carpenter, C. P.: External Contact with Monethyl Ether of Diethylene Glycol (Carbitol Solvent), *Arch. Dermat. & Syph.* **45**:553 (March) 1942.

11. Sulzberger, M. B., and Goodman, J.: Allergy in Dermatology: A Critical Review of Recent Contributions, *J. Allergy* **9**:404, 1934.

12. Coca, A. F.; Walzer, M., and Thommen, A. A.: *Asthma and Hay Fever in Theory and Practice*, Springfield, Ill., Charles C Thomas, Publisher, 1932, p. 386.

were also sensitive to cholesterol. The cholesterol are the active agents in the bases which permit the incorporation of water in "aquaphor" and wool fat.

#### SUMMARY

Nine patients who were sensitive to an oxycholesterol-petrolatum ointment base ("aquaphor") are reported. Eight of the patients were sensitive to cholesterol. The 9 patients also were sensitive to wool fat, "nivea creme" and related substances. Three patients were observed who exhibited reactions of 3 plus to patch tests with "qualatum." Five of the 9 patients had used a sulfathiazole ointment, and 2 had ingested sulfathiazole. In 3 of the patients a history of the therapeutic use of sulfathiazole was not obtained. Sulfathiazole may have acted as a sensitizer or may have had a synergistic sensitizing effect on the bases used in the ointment.

8 East Madison Street.

## CUTANEOUS TESTING IN A CASE OF EXFOLIATIVE DERMATITIS CAUSED BY PENICILLIN

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DURHAM, N. C.

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CINCINNATI

AS THE use of penicillin becomes more widespread and indiscriminate, reports of reactions of cutaneous sensitivity are increasing. Recent reports include those of Goldman, Friend and Mason,<sup>1</sup> and those of Gottschalk and Weiss.<sup>2</sup> The most severe cutaneous reaction, exfoliative dermatitis, was anticipated by Herrell,<sup>3</sup> and 1 case with cutaneous tests has been reported by Goldman and his co-workers.

Opportunity was afforded recently of studying another case of severe exfoliative dermatitis caused by penicillin. Because of the rarity of this reaction and the advanced age of the patient this case is presented.

### REPORT OF A CASE

F. E., a 78 year old white man, was admitted to the Medical Service of the Cincinnati General Hospital on Feb. 27, 1946, acutely ill. Except for seasonal attacks of hay fever since childhood and one attack of cholecystitis in August 1945, he had been well until three days before hospitalization, when there was a sudden onset of pain in the right side accompanied with a chill and temperature of 104 F. Signs of consolidation in the lower lobe of the right lung were demonstrated on physical examination and by roentgenograms. Examination of the culture of the sputum showed the presence of type VII pneumococci. There was also a moderate degree of icterus. A diagnosis of lobar pneumonia and cholecystitis was made. Intramuscular administration of penicillin in a dosage of 20,000 units every three hours was instituted on Feb. 28, 1946. Several different com-

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Crystalline fractions were supplied by Bristol Laboratories, Inc.

This work was aided in part by a grant from Schenley Laboratories, Inc.

From the Department of Dermatology and Syphilology of the College of Medicine of the University of Cincinnati and the Laboratory of Antibiotic Research, Cincinnati General Hospital; Joseph Tamura, director.

1. Goldman, L.; Friend, F., and Mason, L. M.: Eczematous Reactions to Penicillin with Report of Thirteen Cases, *J. A. M. A.* **131**:11 (July 13) 1946.

2. Gottschalk, H. R., and Weiss, R. S.: Epidermal Sensitivity to Penicillin, *Arch. Dermat. & Syph.* **53**:365-371 (April) 1946.

3. Herrell, W. E.: Penicillin and Other Antibiotic Agents, Philadelphia, W. B. Saunders Company, 1945.

mercial brands were used. The clinical course was uneventful until March 3, when a generalized erythematous maculopapular eruption was noted. Because of the extent of the pneumonic process and the age and general condition of the patient, penicillin therapy was not discontinued even though sensitivity to penicillin was suspected. The blood cell count showed the presence of 9,000 white cells and 4,800,000 red cells. Roentgenologic examination revealed "a definite decrease in the amount of previously described pneumonic infiltrate in the right side of the chest." In the following seventy-two hours, vesicles and blebs of various sizes were noted over the thighs, buttocks and abdomen. Rupture of these lesions left large denuded areas. Penicillin therapy was discontinued on March 6, when there was a generalized diffuse erythematous confluent vesicular eruption over the entire body, but most evident over the trunk and extremities. The face was moderately red, with some edema of the eyelids. There was also moderate pretibial edema and generalized lymphadenopathy. The mucous membranes of the mouth showed numerous areas of vesication and erosion. The patient was disoriented, and there were no elicitable complaints except of slight itching. Blood cell counts on March 6 showed 54,000 white cells, 94 per cent neutrophils and 6 per cent

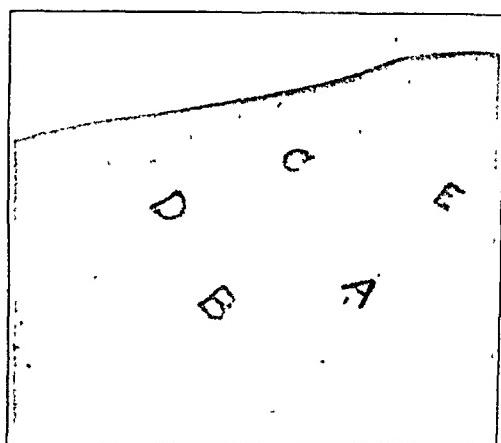


Fig. 1.—Reactions to intradermal tests, left forearm, forty-eight hour reading: *A*, crystalline sodium penicillin K; *B*, crude inactive penicillin; *C*, penicillin-penicillinase; *D*, stock solution of penicillin, and *E*, control (distilled water). Lymphangitic-like extensions at *A* and *D* are evident. The discoloration of the skin at *B* and *C* is due to pigment in the solution.

lymphocytes, with no evidence of eosinophilia. There followed a widespread exfoliation of the epidermis and loss of all the nails, but there was remarkably little alopecia. Convalescence was uneventful except for an entropion of the left lower eyelid. The dermatitis gradually receded over a period of four weeks. The pneumonic process gradually resolved, and the blood picture showed a gradual fall to normal in the white cell count. The patient was discharged from the hospital, free from symptoms of disease, on May 5. It was thought then that as a result of penicillin therapy he had had an eruption of a maculopapular type, which had developed into dermatitis exfoliativa because of the necessity of continuing penicillin therapy.

After the dermatitis had improved, many different types of cutaneous tests were made. Such tests may be grouped briefly under two general headings, intradermal (fig: 1) and contact. Both types of tests were employed because it had been demonstrated previously that persons who are sensitive to penicillin may reveal simultaneously the urticarial, tuberculin and eczematoid types of cutaneous response.

As has been reported before in cases of sensitivity to penicillin, this patient revealed both the urticarial and the tuberculin types of reaction. He did not show any urticarial reaction without a subsequent tuberculin type of reaction.

A biopsy, showing a reaction in seventy-two hours to the intradermal injection of 0.1 cc. of solution containing 200 units of penicillin, revealed definite areas of spongiosis, slight acanthosis and extensive edema of the pars papillaris, with a lymphocytic infiltrate which was perivascular in portions. Only an occasional eosinophil was noted. No giant cells or evidences of tuberculoid structure were observed. There were some fragmentation and separation of the collagen fibers.

TABLE 1.—Intradermal Tests

Material	Amount, Cc.	Concentration, Units	Result
Commercial penicillin A.....	0.1	1,000	+
Commercial penicillin B.....	0.1	1,000	+
Commercial penicillin B (autoclaved).....	0.1	....	-
Crystalline sodium penicillin K.....	0.1	....	+
Sodium penicillin K (autoclaved).....	0.1	....	-
Commercial penicillin B (diluted).....	0.1	200 100 25 15 2.5 0.25 0.025	++ ++ ++ ++ ++ - -
Commercial penicillin B autoclaved (repeat).....	0.1	....	-
Commercial penicillin C (inactive).....	0.1	....	-
Commercial penicillin C and penicillinase.....	0.1	....	-
Penicillin impurities (extract).....	0.1	....	-
Control (distilled water).....	0.1	....	+

TABLE 2.—Patch Tests

Material	Amount	Concentration, Units	Result
Commercial penicillin A.....	0.1 cc.	1,000	+
Crystalline sodium penicillin K.....	0.1 cc.	Approximately 1,000	+
Penicillin impurities.....	0.1 cc.	Approximately 100	-
Crude penicillin solution (inactive).....	0.1 cc.	....	-
Penicillin and penicillinase.....	0.1 cc.	....	+
Penicillin ointment, 1,000 units per Gram.....	Approximately 5 Gm.	....	-
Penicillin ointment base.....	Approximately 5 Gm.	....	-
Crystalline sodium penicillin (autoclaved).....	0.1 cc.	....	-
Solution penicillin B autoclaved).....	0.1 cc.	Approximately 1,000	-

From the data in table 1 it may be seen that this patient was sensitive also to the crystalline penicillin K. At the time of observation, no additional crystalline penicillin fractions were available for testing. An attempt was made to quantitate the reactions, and the end point was observed to be between 2.5 and 0.25 units. It was not possible to obtain closer values. Autoclaving was observed, on assay, to destroy over 90 per cent of the activity of penicillin, and autoclaved penicillin elicited negative reactions even when material was used which had a concentration prior to autoclaving of 0.1 cc. with 1,000 units. This was true of both the solution of commercial penicillin and the solution of crystalline penicillin.

One passive transfer study was made with blood serum by the Prausnitz-Küstner method, in which the donor sites were tested after twenty-four hours and again after five days. These results were negative.

In patch tests the patient was observed to be sensitive to crystalline K (fig. 2). The weak reaction to penicillin impurities may have been due to the penicillin still contained therein. Tests to determine the threshold of activity to penicillin mixtures or ointments were not successful. No patch tests were made at the donor sites of the Prausnitz-Küstner tests.

The patient was observed to exhibit no polyclonal sensitivity to trichophytin, gliotoxin or streptomycin.

Contact mucomembranous tests, after the method of Goldman and Goldman<sup>4</sup> and Goldman and Farrington,<sup>5</sup> were made with crystalline sodium penicillin K. The contact period was twenty-four hours, and the reaction was moderately positive. No conjunctival tests were made because of the presence of conjunctivitis and entropion.

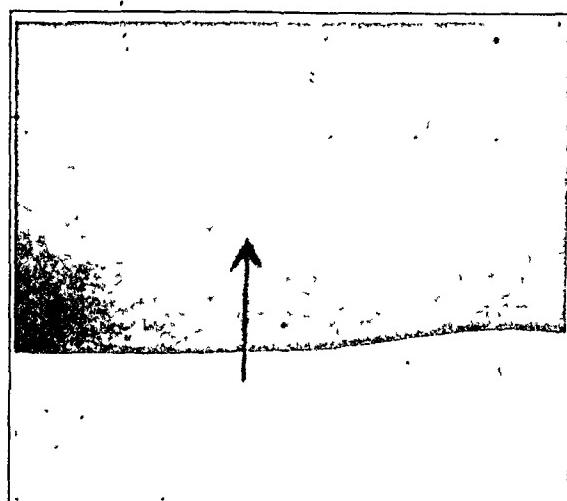


Fig. 2.—Reaction to patch test of right arm with crystalline sodium penicillin K; forty-eight hour reading.

TABLE 3.—*Cutaneous Tests with Additional Fungous Extracts*

Organism Extract	Intradermal Test	Patch Test
Trichophytin 1:30.....	+	—
Gliotoxin 0.2% and cetylpyridium chloride 0.2% in ointment base.....	Not done	—
Streptomycin .....	—	—

#### SUMMARY AND CONCLUSION

Severe dermatitis exfoliativa developed in a white man 78 years of age after parenteral treatment with penicillin for lobar pneumonia. A warning generalized maculopapular eruption first appeared, but continuation of penicillin therapy was necessitated by the severity of the pneu-

4. Goldman, L., and Goldman, B.: Contact Testing of Buccal Mucous Membrane for Stomatitis Venenata, Arch. Dermat. & Syph. 50:79-84 (Aug.) 1944.

5. Goldman, L., and Farrington, J.: Contact Testing of the Buccal Mucous Membrane with Special Reference to Penicillin, Ann. Allergy 4:6 (Nov.-Dec.) 1946.

monia, and the severe cutaneous reaction then developed. After the dermatitis cleared, extensive cutaneous tests were made. The patient was observed to exhibit urticarial and tuberculin types of reactions to different commercial brands of penicillin and to one sample of crystalline sodium penicillin K. Quantitative testing with graded dilutions revealed cessation of cutaneous response between 2.5 and 0.25 units. There was no response to autoclaved material, to crude inactive extracts or to penicillinase-inactivated extracts. No passive transfer reaction could be obtained. Results of patch tests indicated sensitivity to different types of commercial penicillin and to crystalline sodium K. No reactions were obtained with autoclaved material or with diluted mixtures. Tests with other extracts were made: patch tests with trichophytin, gliotoxin and streptomycin elicited negative results, while an intradermal test with trichophytin elicited positive results. This patient demonstrated that severe dermatitis exfoliativa can result from penicillin therapy.

Miss Ethel Barnett, A.B., technician for the Laboratory of Antibiotic Research of the Cincinnati General Hospital, gave technical assistance.

## GRANULAR CELL MYOBLASTOMA

Report of Two Cases

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A BRIKOSOFF<sup>1</sup> in 1926 described a group of peculiar tumors to which he gave the name myoblastic myoma. Other reports of this unusual type of growth followed, particularly in the European literature. Although the location of the majority of lesions which have been reported places them in the province of dermatologists, American dermatologic literature contains, at the time of writing only one paper on the subject, that of Tuta and Schmidt,<sup>2</sup> and the only dermatologic textbook mentioning this form of myoblastic growth is that of Ormsby and Montgomery.<sup>3</sup>

Klempener<sup>4</sup> in 1934 thoroughly reviewed the literature on this subject and reported 44 cases, including 6 of his own. These tumors occurred in all parts of the body. In 1937 Gray and Gruenfeld<sup>5</sup> summarized the literature of 77 cases and added 5 others having the characteristics of myoblastoma. In 1942 Iglauer<sup>6</sup> reported 3 cases of myoblastoma of the larynx, and in 1943 Altman<sup>7</sup> added 3 more cases of this type of tumor occurring in the external auditory canal. Horn and

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From the Skin and Cancer Unit, New York Post-Graduate Medical School and Hospital, Columbia University.

1. Abrikossoff, A. I.: Ueber Myome ausgehend von der quergestreiften willkürlichen Muskulatur, Virchows Arch. f. path. Anat. **260**:215, 1926.

2. Tuta, J. A., and Schmidt, F. R.: So-Called Myoblastoma: Report of Three Cases of Myoblastoma of the Skin and One Case of Myoblastoma of the Trapezius Muscle, Arch. Dermat. & Syph. **46**:225 (Aug.) 1942.

3. Ormsby, O. S., and Montgomery, H.: Diseases of the Skin, ed. 6, Philadelphia, Lea & Febiger, 1943, p. 803.

4. Klempener, P.: Myoblastoma of the Striated Muscle, Am. J. Cancer **20**:324, 1934.

5. Gray, S. H., and Gruenfeld, G. E.: Myoblastoma, Am. J. Cancer **30**:699, 1937.

6. Iglauer, S.: Myoblastoma of Larynx, Ann. Otol., Rhin. & Laryng. **51**:1089, 1942.

7. Altman, F.: Granular Cell Myoblastomas of External Auditory Meatus. Laryngoscope **53**:195, 1943.

Stout<sup>8</sup> in 1943 brought the literature to date with 120 cases and suggested that the tumor be called granular cell myoblastoma, since this term describes the characteristic type of cell of this benign tumor. Crane and Tremblay<sup>9</sup> in 1945 reviewed all the reported cases of myoblastoma and were able to collect the details of 162 cases, including 5 of their own. This thorough and exhaustive summary brings to date all the known cases of myoblastoma, variously described as myoblastic myoma, rhabdomyoma of peculiar cell type, myoblastoma, granular cell myoblastoma and *rhabdomyome granulo-cellulaire*.

We feel that reports of myoblastoma should be added to the American dermatologic literature for several reasons: First, accumulating reports show that it is a not uncommon type of tumor; second, it occurs chiefly in the tongue, skin and mucous membranes; third, although it is doubtless seen by dermatologists, the dermatologic literature is lacking in reports of these cases, and finally, it is important from the viewpoint of differential diagnosis. We shall therefore review the subject briefly and report 2 additional cases.

Striated muscle cell tumors are of two types: one is derived from the adult striated muscle cell and is designated rhabdomyoma, and the other stems from the juvenile muscle cells, or embryonic myoblast, and is called myoblastoma. Abrikossoff felt that the tumor cells were juvenile muscle cells which developed during the process of repair and regeneration following trauma to the striated muscle fibers. Some believe that the cells observed in this tumor are striated muscle fibers which have lost their transverse and longitudinal striations and have become transformed or degenerated into cells of granular cytoplasm. These cells then take on neoplastic qualities. Others feel that the presence of these cells in a part not ordinarily containing muscle tissue is against the theory of degeneration, and they favor the neoplastic formation. These followers suggest that the granular cell myoblastomas may arise from embryonal rests of aberrant myoblastic tissue in places where striated muscle is not normally present. Many writers agree that these cells are of myogenous origin, namely, from primitive myoblasts. They base their opinions on the observation of cross and longitudinal striations within the granular cells or transitions between granular cells and striated muscle fibers. Klemperer<sup>4</sup> described in 1 of his cases an arrangement of granules in transverse rows, suggestive of striations. Horn and Stout,<sup>8</sup> Crane and Tremblay,<sup>9</sup> Thoma<sup>10</sup> and Diss<sup>11</sup> also observed

8. Horn, R. C., Jr., and Stout, A. P.: Granular Cell Myoblastoma, Surg., Gynec. & Obst. **76**:315, 1943.

9. Crane, A. R., and Tremblay, R. G.: Myoblastoma, Am. J. Path. **21**:357, 1945.

10. Thoma, K. H.: Rhabdomyoma of Tongue, Am. J. Orthodontics (Oral Surg. Sect.) **27**:235, 1941.

11. Diss, A.: Le rhabdomyome granulo-cellulaire de la langue, Ann. d'anat. path. **7**:1071, 1930.

longitudinal striations, suggestive of myofibrils, and parallel cross striations in isolated granular cells. The last word has not been spoken regarding the origin of these tumors, but some day this may be clarified to the satisfaction of all.

Granular cell myoblastomas are commonest between the ages of 30 and 50, although they may occur at any age. Males and females are equally affected. The tumors usually appear as pea-sized nontender nodules, varying from 1 to 2 cm. or larger in diameter. They are discrete rounded or nodular firm masses which protrude from the surface and are pinkish to yellowish. Clinically myoblastoma cannot be differentiated from xanthoma or fibroma, but histologically it is a distinct entity.

Microscopically, the characteristic cells are large, pale and polyhedral, containing acidophilic granular cytoplasm. They vary from 20 to 60 microns in diameter, and even larger ones have been reported. The nuclei are small, round or oval and somewhat vesicular. At times more than one nucleus are present. The nuclei are usually placed centrally, and in some instances nucleoli have been observed. At times ribbon-like or irregular syncytial masses may occur. Alveolar arrangement of some of the cells has also been noted. Hartz<sup>12</sup> presented a case in which the organoid pattern of growth was entirely present. The neoplastic elements stand out from the surrounding muscle because of their lighter color and pale-staining cells. The cells are surrounded by delicate strands of connective tissue fibrils. Sudan and other fat stains reveal no fat, distinguishing them from the foam cells of xanthoma. Some of the tumors are definitely encapsulated. In some cases, the capsule is absent and the cells blend with the adjacent muscle fibers.

Myoblastomas are generally benign tumors. This has been confirmed by most observers. Many of these tumors which have been reported as showing evidence of malignancy are thought to be rhabdomyosarcomas. Ravich, Stout and Ravich<sup>13</sup> did report a granular cell myoblastoma of the urinary bladder which became malignant and metastasized, but this occurrence is an exception rather than the rule.

After removal of some of these tumors, local recurrences have been noted. This is caused by the lack of encapsulation, as a result of which tumor cells infiltrate between the striated muscle fibers. Myoblastomas should therefore be excised with a fair margin of safety, and then a biopsy should be made. Histologic examination will determine the type of tumor and whether it has been removed in its entirety. That a single nonulcerated lesion on the tongue or skin is benign is usually

12. Hartz, P. H.: So-Called Granular Cell Myoblastoma of Thigh with Organoid Structure, Am. J. Clin. Path. **14**:582, 1944.

13. Ravich, A.; Stout, A. P., and Ravich, R. A.: Malignant Granular Cell Myoblastoma Involving the Urinary Bladder, Ann. Surg. **121**:361, 1945.

taken for granted. However, when there is a recurrence one begins to wonder whether a mistake in diagnosis has been made. This can usually be clarified by histologic examination.

One should also be aware of the fact that when these growths occur in the skin and beneath the mucosal surfaces, a proliferation of squamous epithelium occurs. The epithelium covering these areas at times will present epithelioma-like proliferative changes, and, as a result, squamous cell epithelioma has been erroneously diagnosed. This, too, can be prevented by a histologic examination of the tissue. We strongly urge biopsies of lesions of the tongue, especially when there is a recurrence after removal of what appeared to be a benign lesion.

Myoblastomas have a predilection for the proximal part of the alimentary tract and upper respiratory tract. The tongue is the com-

#### *Summary of Cases of Myoblastoma Reported in the Literature*

Site	Number
Tongue.....	62*
Skin.....	18*
Subcutis.....	17
Muscle.....	13
Maxilla.....	11
Larynx and vocal cords.....	8
Breast.....	8
Mandible.....	6
Lip.....	4
Ear.....	3
Trachea and bronch.....	3
Alveolar process.....	2
Others.....	9
Total.....	164

\* This includes our case.

most frequent site for these tumors, although they have been found widely distributed throughout the body. Of 164 cases recorded (including the 2 about to be reported), in 62 the myoblastomas were located in the tongue. The skin and subcutis are the next most frequent sites. Crane and Tremblay tabulated the site of occurrence as listed in the accompanying table.

CASE 1.—M. M., a man aged 44, born in the United States, first noticed a small lump on the right side of his tongue about a year previous to examination. The lesion grew slowly, but there were no subjective symptoms other than the feeling of a mass. Examination revealed a small oval tumor on the anterior dorsal surface of the tongue near the right border, measuring about 0.75 cm. in its longest diameter. The color was that of normal mucous membrane or perhaps slightly paler. The papillae were absent over the tumor. There was no adenopathy or interference with mastication, and no changes in sensation were manifested. The tissues surrounding the lesion were anesthetized with procaine hydrochloride, and with the cutting current of the high frequency machine the tumor was excised *in toto*. The base of the wound was electrodesiccated.

Microscopic examination of the specimen showed the epithelium to be that of mucous membrane, with no granular layer present. Tumor cells were seen beneath the epithelium, extending downward between the muscle fibers. The cells were large and pale staining, with granular cytoplasm and a well defined cell membrane. One or more nuclei were present in each cell. With high power magnification, the large round and polygonal cells could be clearly seen. They varied from 20 to 60 microns in size. The cells were clearly outlined, and the cytoplasm was com-

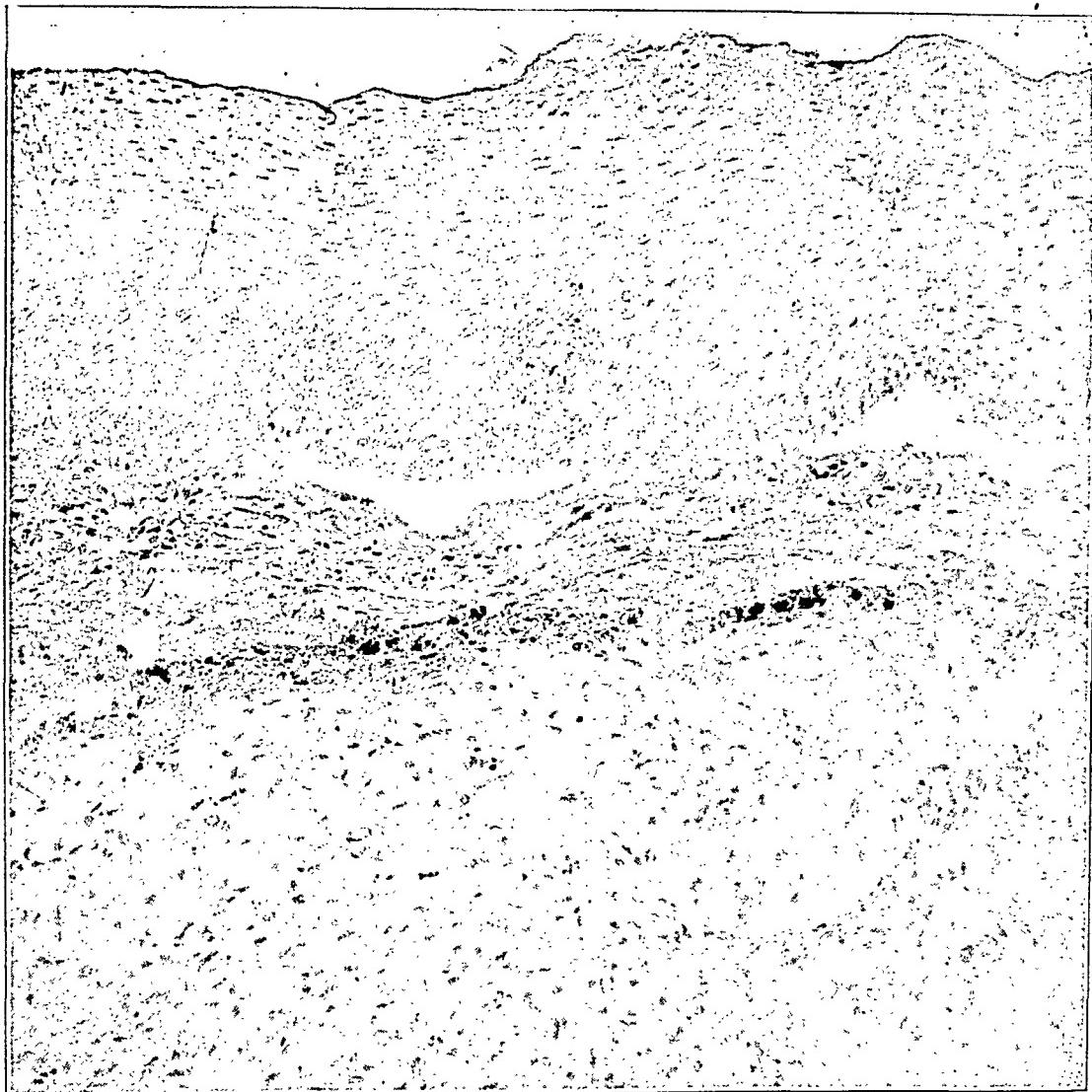


Fig. 1.—The surface of the mucous membrane overlying the tumor is essentially normal. The tumor cells are pale staining, large, oval or round and contain one to several nuclei (hematoxylin and eosin stain:  $\times 175$ ).

posed of densely packed granules, without definite arrangement. In each cell was a round or angular nucleus of a vesicular nature; some cells contained more than one nucleus, and some nuclei contained more than one nucleolus. A fine network of connective tissue fibers surrounded these large cells. These observations are consistent with those of granular cell myoblastoma.

CASE 2.—I. W.,<sup>14</sup> a man aged 40, came to the Skin and Cancer Unit on March 19, 1946, complaining of a nodule, about the size of a marble, on the dorsum of the index finger of the right hand. Clinically it appeared to be a neurofibroma. The nodule was excised and sent to the laboratory for examination.

Dr. Charles Sims reported that the epidermis revealed no noteworthy characteristics. Throughout the upper, middle and deep layers of the corium were

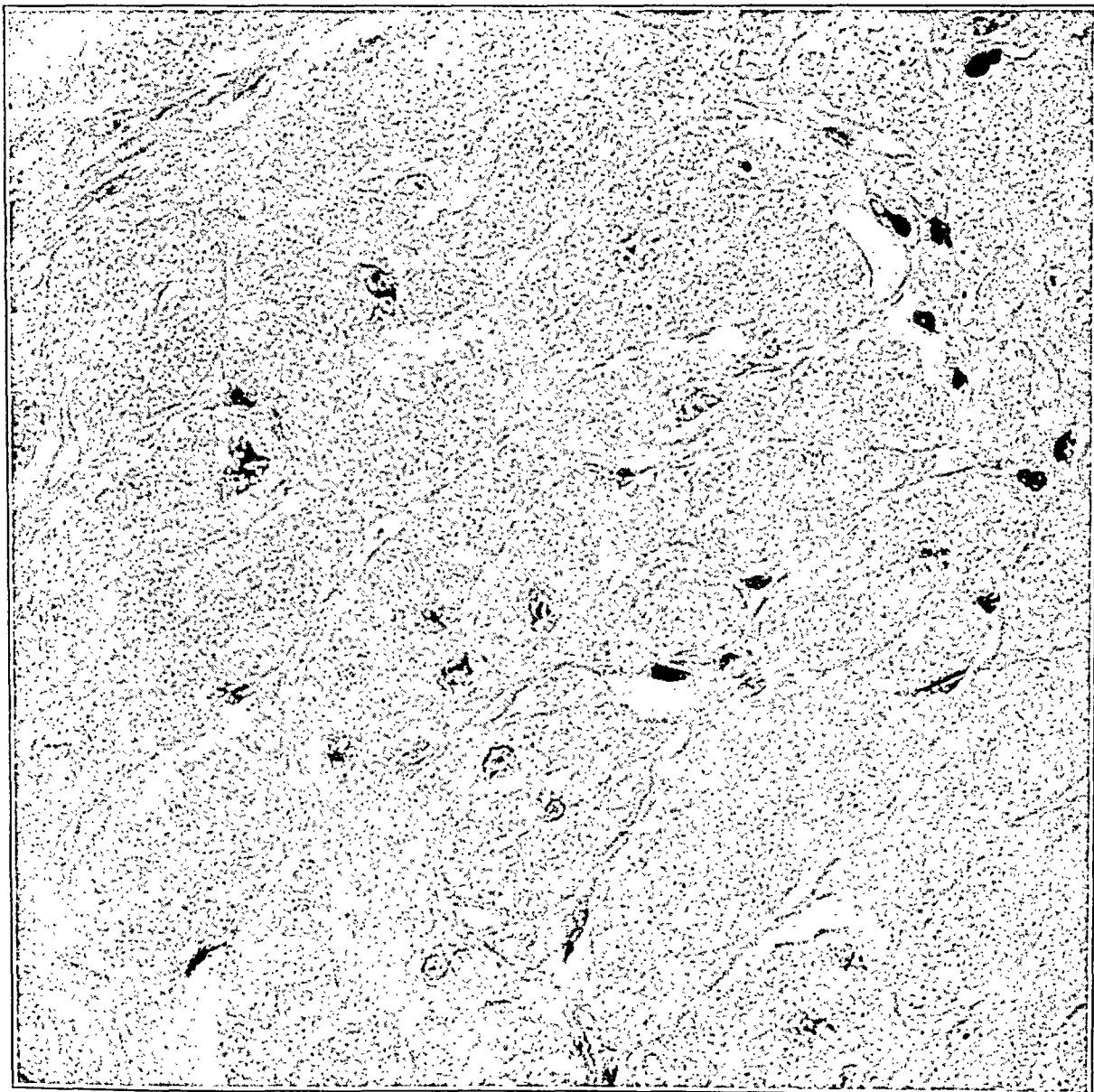


Fig. 2.—Typical tumor cells, showing one to several nuclei in each cell, the granular appearance of the cytoplasm and the distinct cellular outlines. The cells are separated from one another by fine connective tissue fibrils (hematoxylin and eosin stain;  $\times 375$ ).

numerous cellular masses of varying sizes and shapes, which stained a little paler than the surrounding normal collagen. These masses were apparently present in

14. Permission was granted to report this case from the service of Max Scheer, M.D., Skin and Cancer Unit, Post-Graduate Medical School and Hospital.

the interstitial lymphatic spaces. Examined under high power magnification they were apparently composed of well defined and rather large cells, some larger than others, containing a large round or oval vesicular nucleus and granular cytoplasm. Other inflammatory cells were not present to any degree. In one or two instances, multinucleated cells could be observed. No muscle was seen in this section. With the Van Gieson stain the granular cells were yellowish, in contrast to the surrounding collagen, which was pink. (Dr. M. Richter and Dr. W. Sachs helped to interpret the slides.)

#### SUMMARY

The literature on myoblastoma is briefly reviewed, and the genesis and histologic structure of this type of striated muscle cell tumor are discussed. The locations of the reported cases are tabulated, and 2 additional cases are described.

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## CHEMISTRY OF PALMAR SWEAT

### III. Reducing Substances (Glucose)

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AND

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OUR PREVIOUS studies on the chemistry of palmar sweat, collected from the openings of the sweat ducts of the finger tips of normal subjects,<sup>1</sup> indicated that both chloride<sup>2</sup> and urea<sup>3</sup> are more concentrated in the sweat when the sweat gland is functioning intermittently than when it is functioning continuously.

This report deals with similar studies on the concentration of glucose in palmar sweat, or rather of reducing substances in the sweat, since the analytic method<sup>4</sup> used is not specific for glucose alone.

There are conflicting reports<sup>5</sup> in the literature regarding the concentration of sugar in the sweat as well as regarding its presence or

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From the Section on Dermatology and Syphilology (Dr. Lobitz), and the Division of Clinical Biochemistry (Dr. Osterberg), Mayo Clinic.

1. Lobitz, W. C., Jr., and Osterberg, A. E.: Chemistry of Palmar Sweat: Preliminary Report; Apparatus and Technics, *J. Invest. Dermat.* **6**:63-73 (Feb.) 1945.

2. Lobitz, W. C., jr., and Osterberg, A. E.: Chemistry of Palmar Sweat: II. Chloride, *Arch. Dermat. & Syph.* **56**:462-467 (Oct.) 1947.

3. Lobitz, W. C., Jr., and Osteberg, A. E.: Chemistry of Palmar Sweat: IV. Urea. *Arch. Dermat. & Syph.*, this issue, p. 827.

4. Walker, A. M., and Reisinger, J. A.: Quantitative Studies of the Composition of Glomerular Urine: IX. The Concentration of Reducing Substances in Glomerular Urine from Frogs and Necturi Determined by Ultramicro-Adaptation of the Method of Sumner; Observations on the Action of Phlorhizin, *J. Biol. Chem.* **101**:223-237 (June) 1933.

5. (a) Usher, B., and Rabinowitch, I. M.: Excretion of Sugar in Sweat: Its Relationship to Eczema, *Arch. Dermat. & Syph.* **16**:706-713 (Dec.) 1927.

(b) McSwiney, B. A.: The Composition of Human Perspiration, *Proc. Roy. Soc. Med.* **27**:839-848 (May) 1934. (c) Silvers, S.; Forster, W., and Talbert, G. A.: Simultaneous Study of the Constituents of the Sweat, Urine and Blood, Also Gastric Acidity and Other Manifestations Resulting from Sweating: VI. Sugar, *Am. J. Physiol.* **84**:577-582 (April) 1928. (d) Schulze, W., and Kunz, K.: Ueber den Anteil des als Osazon bestimmten Zuckers und einiger anderer Substanzen am Reduktionsvermögen des Schweißes, *Arch. f. Dermat. u. Syph.* **181**:

*(Footnote continued on next page)*

absence in the sweat in normal states and in disease. All previous studies of this type have been carried out on general body, or thermal-regulating, sweat. The variations in the reports seem dependent in part on the method of collection of sweat, the manner of handling the sweat after collection and the analytic method used. This fact is illustrated, each from a different approach, by several authors: Usher and Rabinowitch<sup>5a</sup> stated that there are appreciable differences in the content of sugar of general body sweat containing epithelial debris and so forth before and after the sweat is cleared with kaolin. McSwiney<sup>5b</sup> observed that the action of bacteria present in the sweat decreased the concentration of sugar in the sweat. Silvers, Forster and Talbert,<sup>5c</sup> Schulze and Kunz<sup>5d</sup> and Schulze<sup>5e</sup> showed variations in the concentration of sugar in the sweat when different analytic methods were used. The values for sugar reported for general body, or thermal-regulating, sweat vary from 0 to 40 mg. of glucose per hundred cubic centimeters of sweat.<sup>5</sup> Schulze and Kunz showed that although reducing substances are measurable in sweat, when the sugar is determined as osazone there is no glucose present.

It seems agreed, with one exception,<sup>5h</sup> that there is no relation between sugar in the blood and sugar in the sweat in normal subjects whose blood sugar has been elevated nor in subjects with elevated levels of blood sugar resulting from diabetes mellitus.<sup>6</sup>

In our studies on palmar sweat the method of collection<sup>1</sup> is such that only pure sweat, uncontaminated by epithelial cells, oils and so forth, is obtained. The procedure of collection and analysis for this study is the same as that used in the study on urea,<sup>3</sup> that is, whenever possible we collected two separate specimens of sweat from the same subject during the half-hour period of collection. At the end of the period specimens of blood and urine were obtained. The volumes of sweat were measured by the manipulative technic of Richards, Bordley

486-494 (Dec.) 1940. (e) Schulze, W.: Ueber den "Zucker" gehalt auf der Haut, im Hautdialysat und im Schweiß, ibid. **181**:471-485 (Dec.) 1940. (f) Usher, B.: Human Sweat as Culture Medium for Bacteria: Preliminary Report, Arch. Dermat. & Syph. **18**:276-280 (Aug.) 1928. (g) Mosher, H. H.: Simultaneous Study of Constituents of Urine and Perspiration, J. Biol. Chem. **99**:781-790 (Feb.) 1933. (h) Marchionini, A., and Ottenstein, B.: Stoffwechselveränderungen im Schwitzbad bei Hautgesunden und Hautkranken: II. Einfluss auf den Kohlehydrate- und Lipoidstoffwechsel. Klin. Wchnschr. **10**:971-973 (May 23) 1931. (i) Williams, J. W.: The Pathological Physiology of the Kidneys (and Sweat Glands) in Infections, Urol. & Cutan. Rev. **44**:47-49 (Jan.) 1940. (j) Ito, S.: Significance of Blood Sugar During Sweat Secretion in Man, J. Orient. Med. (Abstr. Sect.) **28**:61 (April) 1938.

6. Usher and Rabinowitch.<sup>5a</sup> Silvers, Forster and Talbert.<sup>5c</sup> Schulze.<sup>5e</sup>

and Walker.<sup>7</sup> The analyses for reducing substances in the palmar sweat were made by the capillary tube colorimetry method of Walker and Reisinger<sup>4</sup> (using dinitrosalicylic acid reagent, Sumner's method), which was recently adapted by us<sup>8</sup> to the spectrophotometer. The estimations of glucose in the blood were made by the method of Folin and Wu.<sup>9</sup> The urine was tested qualitatively for the presence of reducing substances by Benedict's qualitative copper sulfate solution.

Five normal men and 5 normal women between the ages of 22 and 35 years were studied. From this group a total of forty-seven successful collections and analyses of palmar sweat were made (table 1). Nineteen of the collections (from 4 men and 3 women) were of the so-called profuse physiologic type, in which the sweat gland was working continuously as in thermal-regulating sweat. Twenty-eight collections (5 men and 3 women) were of the so-called intermittent physiologic type, in which the sweat droplets appeared at the openings of the sweat duct intermittently and the sweat gland apparently rested during the intervals between such work. In seven instances we were able to obtain both physiologic types of palmar sweating, separately from the same subject and during a single half-hour period of collection. In no instance was there any consistent significant difference in the concentration of reducing substances in the two different physiologic types of palmar sweat. The mean value for reducing substances in "profuse" sweat was 3.08 mg. of glucose per hundred cubic centimeters (maximum 11 mg. and minimum 0), the median was 2.6 mg. of glucose per hundred cubic centimeters and the mode 0. The intermittent type of sweat gave a mean value of 2.86 mg. of glucose per hundred cubic centimeters (maximum 16 mg. and minimum 0), a median of 0 and a mode of 0. The levels for glucose in the blood were normal with a mean of 86 mg. per hundred cubic centimeters (maximum 100, minimum 74). All specimens of urine yielded a negative reaction in qualitative tests for reducing substances.

From these studies it would seem that the sugar barrier in the palmar sweat gland is most efficient at normal levels of sugar in the blood. These values for reducing substances are lower than the average

7. Richards, A. N.; Bordley, J., III, and Walker, A. M.: Quantitative Studies of the Composition of Glomerular Urine: VII. Manipulative Technique of Capillary Tube Colorimetry, *J. Biol. Chem.* **101**:179-191 (June) 1933.

8. Lobitz, W. C., Jr., and Osterberg, A. E.: The Use of the Spectrophotometer in Capillary Tube Colorimetry for the Determination of Reducing Substances (Glucose), Chlorides, Ammonia Nitrogen, Uric Acid, and Creatinine, *J. Invest. Dermat.* **7**:135-144 (June) 1946.

9. Folin, O., and Wu, H.: A System of Blood Analysis: A Simplified and Improved Method for Determination of Sugar, *J. Biol. Chem.* **41**:367-374 (March 20) 1920.

values for general body, or thermal-regulating, sweat reported in the literature and agree more closely with values on general body sweat reported by Schulze<sup>5c</sup> and Schulze and Kunz.<sup>5d</sup>

TABLE 1.—Reducing Substances in Blood and Palmar Sweat of Normal Persons\*

Subject	Age, Years	Sex	Month, Day, 1945	Physiologic Type of Sweating	Volume of Sweat, in 0.35 Mm. <sup>†</sup>			Reducing Substances (Glucose), Mg. per 100 Cc.
					Tube, per 50 Glands, Min. Mm.	Volume per Minute from 50 Glands, Min. Cc.	Volume per Minute of Urine per Minute Palmar Sweat Blood	
R. O.....	25	F	11/28	Profuse	0.49	0.25	6.4	86
			11/29	Profuse	1.02	....	8.8	..
			11/29	Profuse	1.98	0.81	2.0	78
			11/30	Profuse	2.04	....	2.0	..
			11/30	Profuse	1.15	0.32	2.0	95
D. M.....	22	F	11/28	Intermittent	0.19	0.30	0.4	84
			11/29	Profuse	0.56	....	3.8	..
			11/29	Profuse	0.78	0.34	2.0	86
			11/30	Intermittent	0.08	....	12.0	..
			11/30	Intermittent	0.18	0.31	16.0	86
J. M.....	22	F	12/ 1	Intermittent	0.10	....	5.3	..
			12/ 3	Intermittent	0.10	0.25	0.0	90
			12/ 5	Intermittent	0.03	0.43	8.0	85
			12/ 5	Intermittent	0.03	0.85	0.0	83
G. S.....	27	M	12/ 3	Intermittent	0.09	1.37	13.0	86
			12/ 4	Profuse	0.60	....	4.0	..
			12/13	Intermittent	0.08	0.87	0.0	83
			12/13	Intermittent	0.24	1.28	0.0	83
E. W.....	35	F	12/ 4	Profuse	0.25	....	2.6	..
			12/ 5	Intermittent	0.08	0.66	0.0	90
			12/ 5	Intermittent	0.12	....	0.0	..
			12/10	Intermittent	0.04	0.70	0.0	86
R. M.....	28	M	12/ 5	Intermittent	0.71	0.60	0.0	88
			12/ 5	Intermittent	0.05	0.58	0.0	83
			12/11	Intermittent	0.03	....	0.0	..
			12/11	Intermittent	0.17	1.00	0.0	95
P. C.....	34	M	12/ 8	Intermittent	0.13	....	0.0	..
			12/10	Profuse	0.37	1.20	0.0	90
			12/11	Intermittent	0.13	....	0.0	..
			12/12	Profuse	0.05	0.28	11.0	83
G. N.....	27	F	12/14	Profuse	0.85	4.4	3.6	74
			12/15	Profuse	0.48	....	3.2	..
			12/17	Profuse	0.31	5.1	0.0	83
			12/18	Intermittent	0.05	0.50	0.0	74
U. S.....	32	M	12/13	Intermittent	0.03	0.44	0.0	100
			12/14	Intermittent	0.01	0.77	0.0	83
			12/17	Intermittent	0.54	0.60	4.5	85
			11/29	Intermittent	0.13	....	10.0	..
H. T.....	28	M	11/28	Profuse	0.17	0.80	5.0	95
			11/29	Intermittent	0.25	1.10	0.0	95
			12/18	Profuse	0.16	1.10	0.0	..

\* All specimens of urine yielded a negative reaction for glucose with Benedict's qualitative solution.

† Inside diameter.

In order to raise the levels of sugar in the blood in normal subjects we fed 100 Gm. of glucose by mouth on three occasions to subjects (2 women, D. M. and G. N.) who were known to be able to deliver

profuse dilute palmar sweat on request. Specimens of blood and urine were collected at the same time (table 2). There was no spilling of glucose into the sweat in any of the specimens. The peak values for reducing substances in the blood were 168, 139 and 111 mg. per hundred cubic centimeters. The specimens of urine were negative for glucose by qualitative test.

To learn whether the sugar barrier in the palmar sweat gland was efficient at even higher levels of sugar in the blood we next gave 20 Gm. of glucose (20 per cent solution) intravenously to 3 normal men and

TABLE 2.—Reducing Substances in Blood, Sweat and Urine Before and After Oral Administration of Glucose

Subject	Age, Years	Sex	Time After Oral Administration of Glucose		Reducing Substances (Glucose), Mg. per 100 Cc.		Urine, Benedict's Qualitative Reaction
			Hours	Minutes	Blood	Palmar Sweat*	
Fasting Values							
D. M.....	22	F	..	..	86	0	—
After Oral Administration of 100 Gm. Glucose (20 per Cent Solution)							
			0	48	149	0	—
			1	20	168	0	—
			1	50	153	0	—
Fasting Values							
D. M.....	22	F	..	..	95	0	—
After Oral Administration of 100 Gm. Glucose (20 per Cent Solution)							
			0	35	139	0	—
			1	10	107	0	—
Fasting Values							
G. N.....	27	F	..	..	86	0	—
After Oral Administration of 100 Gm. Glucose (20 per Cent Solution)							
			0	40	111	0	—
			1	30	74	0	—
			2	15	82	0	—

\* All specimens of sweat were of the so-called profuse physiologic type.

3 normal women (table 3) who could also deliver profuse palmar sweat. Samples of sweat and blood and specimens of urine were collected simultaneously, as in a glucose tolerance test. The peak values for glucose in the blood varied between 214 and 252 mg. per hundred cubic centimeters. G. N. had a peak value of glucose in the sweat of 4 mg. and D. M. a peak value of 18 mg. per hundred cubic centimeters. Both of these subjects were known to have higher than our average level for reducing substances in the sweat when fasting (table 1). The sweat glands of the other 4 subjects maintained an absolute barrier against glucose, and all samples of sweat collected from them were negative for reducing substances. The specimens of urine reduced

TABLE 3.—Reducing Substances in Blood, Sweat and Urine Before and After the Intravenous Administration of Glucose

Subject	Age, Years	Sex	Time After Intravenous Injection of Glucose, Minutes	Reducing Substances		Urine, Benedict's Qualitative Reaction
				Mg. per 100 Cc.	Palmar Sweat*	
Fasting Values						
G. S.....	27	M	..	95	0	—
After Intravenous Injection of 20 Gm. Glucose (20 per Cent Solution)						
			5	214	0	..
			10	180	0	++
			30	132	0	+
			60	107	0	—
Fasting Values						
G. N.....	27	F	..	103	0	—
After Intravenous Injection of 20 Gm. Glucose (20 per Cent Solution)						
			3.5	252	4	..
			15	173	0	+
			35	120	0	—
			60	100	0	—
Fasting Values						
D. M.....	22	F	..	100	0	—
After Intravenous Injection of 20 Gm. Glucose (20 per Cent Solution)						
			3	252	18	..
			15	173	8	++
			30	130	4	..
			60	100	0	+
Fasting Values						
P. C.....	34	M	..	95	0	—
After Intravenous Injection of 20 Gm. Glucose (20 per Cent Solution)						
			5	252	0	..
			10	...	..	+++
			15	173	0	..
			35	120	0	+
			60	83	0	—
Fasting Values						
R. M.....	28	M	..	115	0	—
After Intravenous Injection of 20 Gm. Glucose (20 per Cent Solution)						
			5	235	0	..
			9	...	..	+++
			17	158	0	..
			25	..	..	+++
			35	93	0	..
			60	100	0	+
Fasting Values						
R. C.....	25	F	..	95	0	—
After Intravenous Injection of 20 Gm. Glucose (20 per Cent Solution)						
			5	238	0	..
			10	...	..	++++
			25	152	0	+
			60	90	0	—

TABLE 3.—Reducing Substances in Blood, Sweat and Urine Before and After the Intravenous Administration of Glucose—Continued

Subject	Age, Years	Sex	Time After Intravenous Injection of Glucose, Minutes	Reducing Substances (Glucose), Mg. per 100 Cc.		Urine, Benedict's Qualitative Reaction
				Blood	Palmar Sweat*	
Fasting Values						
H. F.†.....	18	F	..	74	0	—
After Intravenous Injection of 20 Gm. Glucose (20 per Cent Solution)						
			5	235	0	++
			20	195	0	+++
			45	139	0	..
			70	100	0	—
Fasting Values						
R. F.†.....	54	F	..	100	4	—
After Intravenous Injection of 20 Gm. Glucose (20 per Cent Solution)						
			5	281	4	..
			15	...	..	++

\* All specimens of sweat were of the so-called profuse physiologic type.

† Patients who had dyshidrotic dermatitis of the hands.

Benedict's qualitative solution to reactions of 1 to 4 plus (equivalent to 500 to 3,000 mg. of glucose per hundred cubic centimeters) when the levels of blood sugar were at their peaks.

When profuse palmar sweat was studied similarly (table 3, H. F. and R. F.) from 2 subjects suffering from so-called dyshidrotic dermatitis of the hands, the results were similar.

TABLE 4.—Fasting Levels of Reducing Substances (Glucose) in Blood, Palmar Sweat and Urine of Patients Who Had Prolonged Uncontrolled Diabetes Mellitus

Subject	Age, Years	Sex	Physiologic Type of Sweating	Reducing Substances, Mg. per 100 Cc.		Urine, Benedict's Qualitative Reaction
				Blood	Palmar Sweat	
A. K. ....	49	F	Profuse	210	0.0	++
R. R. ....	53	M	Profuse	226	0.0 (2.16 per cent glucose)	+

All these studies were made under acute conditions, and the question remained whether similar results would be obtained if the blood sugar were elevated continuously over a prolonged period. We therefore collected palmar sweat from 2 subjects who had uncontrolled diabetes mellitus. At the time of our studies, their disease had never been previously treated with diet or insulin and the levels of glucose in the blood in both subjects were more than 200 mg. per hundred cubic centimeters. The samples of their palmar sweat did not contain glucose (table 4).

## SUMMARY

Forty-seven specimens of palmar sweat, collected for the study of reducing substances, were grouped into two physiologic types: (1) profuse and (2) intermittent. In seven instances both physiologic types of palmar sweat were obtained on request within a half-hour period from the same subject. There was no significant difference in the concentration of reducing substances in the two types.

The sugar barrier in the sweat gland was efficient for the most part in normal subjects with normal values for blood sugar as well as with raised levels for blood sugar. Studies on 2 subjects who had dermatitis of the hands gave similar results. Studies on 2 subjects who had uncontrolled untreated diabetes mellitus and whose levels for blood sugar had been elevated for a prolonged period also failed to show any spilling of glucose into the palmar sweat.

There was no relation between the concentration of reducing substances in the sweat and the values for glucose in blood or urine. The majority of analyses of palmar sweat revealed no reducing substances present when the values for blood sugar were normal or elevated.

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## CHEMISTRY OF PALMAR SWEAT

### IV. Urea

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AS PREVIOUSLY stated,<sup>1</sup> studies on the chemistry of palmar sweat, collected from normally functioning individual sweat glands, were undertaken with the hope that the information so gained would eventually lead to a better understanding of the "abnormal" sweat gland.

As previously reported,<sup>1a</sup> the chamber specially designed for these studies made it possible not only to collect pure uncontaminated sweat directly from the openings of the sweat ducts but also to observe the rate and manner of secretion of sweat from the individual ducts during the collection. Such observations<sup>1b</sup> have made it possible to classify into physiologic types the manner in which palmar sweat is secreted: profuse, intermittent and a combination of these two types. These studies on palmar sweat showed that the concentration of chloride is low and equal to that of thermal-regulating body sweat when the gland secretes profusely, but when it functions intermittently the palmar sweat gland can concentrate chloride as efficiently as the excreting units of the kidney.

The content of urea in general body, or thermal-regulating, sweat in both health and disease has been studied for various reasons by many observers.<sup>2</sup> The previously reported concentrations of urea in this

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From the Section on Dermatology and Syphilology, (Dr. Lobitz), and the Division of Clinical Biochemistry (Dr. Osterberg), Mayo Clinic.

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*(Footnote continued on next page)*

profuse dilute sweat vary between the extremes of 23.5 mg. and 400 mg. per hundred cubic centimeters of sweat (11 to 186 mg. of urea nitrogen per hundred cubic centimeters of sweat). The average range, however, is between 64 and 128 mg. of urea per hundred cubic centimeters (30 to 60 mg. of urea nitrogen per hundred cubic centimeters). All observers who studied the concentration of urea in the blood simultaneously with that in the sweat agreed that the sweat glands are capable of concentrating urea above the level of urea in the blood. Whether this is a result of the concentrating ability of an excreting unit or whether it is a property of a selective secreting unit is yet to be determined.

In our studies on the urea content of palmar sweat, the analytic method of Walker and Hudson was used.<sup>3</sup> In this procedure volumes of sweat even smaller than those necessary for determination of chloride could be used. In addition, by this time we had learned many methods of stimulating palmar sweating. Even more important, the persons repeatedly used as experimental subjects in these studies had also learned many ways to stimulate palmar sweating at a given time. For these reasons, in most instances, we were able to collect two separate specimens of sweat during a half-hour period. In some cases it was possible to obtain a specific type of sweating at a specific time as desired.

At the end of the period of collection of sweat, specimens of blood and urine were obtained. The specimen of urine was that amount of urine that had accumulated in the bladder during the same half-hour period during which the specimens of sweat were collected. (The volume of urine is expressed as cubic centimeters excreted per minute.) A

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single collection of sweat was continued only as long as was necessary to obtain a volume of sweat large enough for study. (The volume of sweat is expressed as length in millimeters, in a capillary tube having a uniform inside diameter of 0.35 mm. of the sweat collected per minute from fifty sweat glands.) The subjects had fasted for four hours.

The volumes of sweat were measured by the manipulative technic of Richards, Bordley and Walker,<sup>4</sup> the analyses for urea in the sweat were made by the ultramicro capillary tube method of Walker and Hudson,<sup>5</sup> and for the analyses for urea in the blood and urine the method of Van Slyke and Cullen<sup>5</sup> was used. The work was carried out during the spring when thermal-regulating sweat was absent during average activity. Eight men and 11 women between the ages of 21 and 48 years were studied. From these a total of seventy-seven successful collections and analysis of sweat was obtained.

The physiologic types of palmar sweating fell into two groups. Figure 1 illustrates these two types graphically: (1) the profuse con-

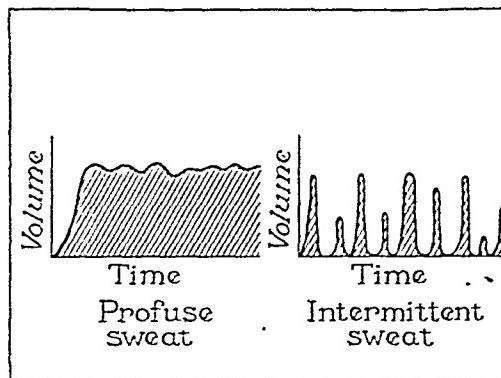


Fig. 1.—The manner of output from an individual sweat gland, the so-called profuse and intermittent physiologic types of palmar sweating.

tinuous output of sweat, (2) the intermittent output of sweat, with the sweat gland resting between bursts. We have pointed out<sup>1b</sup> that individual collections of palmar sweat could be compared on the basis of physiologic type even though the variability of secretion from the individual gland made it unwise to compare collections of sweat according to volume of sweat secreted (table 1).

A total of twenty-seven collections of the profuse type of sweat (fig. 2) were obtained from 3 men and 7 women. The average value for urea in the sweat was 68 mg. per hundred cubic centimeters (minimum 32 and maximum 193 mg. urea per hundred cubic centimeters of sweat).

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TABLE 1.—Values for Urea in Sweat, Blood and Urine

Subject	Age, Years	Sex	Day of Month, May 1946	Physio- logic Type of Sweating	Volume of Sweat, as			Urea		
					Tube per Minute, from 50 Glands	Output per Minute, Cc., per Output	Urine, as Mm. in 0.35 Mm. I. D.*	Sweat, Mg. per 100 Cc.	Blood, Mg. per 100 Cc.	Urine, Gm. per 100 Cc.
R. C.....	24	F	7	P†	0.68	0.80	37	22	2.6	
			9	P	0.75	...	66	...	...	
			11	P	0.34	1.74	40	14	0.6	
			11	P	0.17	...	40	...	...	
A. M.....	41	F	7	I‡	0.05	0.40	130	26	2.3	
			9	I	0.26	...	81	...	...	
			11	P	0.40	1.81	40	22	0.4	
			11	P	0.28	...	67	...	...	
J. F.....	27	F	7	I	0.01	0.83	466	26	0.7	
			7	P	0.58	0.46	60	26	2.4	
			8	P	0.12	...	67	...	...	
			12	P	0.40	0.57	67	28	2.6	
D. M.....	22	F	7	P	0.35	...	59	...	...	
			8	P	0.09	0.80	250	22	1.0	
			12	I	0.06	...	250	...	...	
			12	I	0.37	1.48	112	30	1.0	
B. M.....	48	F	8	I	0.12	0.58	140	24	1.1	
			10	P	0.40	...	59	...	...	
			22	P	0.13	0.44	60	18	0.7	
			22	P	0.43	...	33	...	...	
D. R.....	33	M	8	I	0.04	0.04	370	24	1.4	
			12	I	0.15	0.97	294	28	1.2	
			19	I	0.13	...	213	...	...	
			19	P	0.22	1.33	346	28	1.2	
G. N.....	27	F	9	P	0.37	0.90	176	18	1.3	
			11	P	0.40	0.90	47	18	1.3	
			11	I	0.28	...	50	...	...	
			14	P	0.13	4.6	75	20	0.4	
B. B.....	22	F	9	I	0.12	...	60	...	...	
			22	I	0.33	...	103	...	...	
			24	I	0.20	4.4	150	28	0.4	
			24	I	0.03	0.4	310	24	2.6	
E. W.....	35	F	9	I	0.03	3.9	452	26	1.0	
			15	I	0.03	0.3	200	14	1.6	
			15	I	0.09	0.7	193	16	1.0	
			15	I	0.07	...	180	...	...	
R. C.....	27	M	14	I	0.02	0.34	590	38	1.8	
			16	I	0.04	0.64	620	24	1.4	
			15	I	0.12	0.89	480	34	2.2	
			19	I	0.13	0.49	454	32	2.9	
H. T.....	28	M	15	I	0.05	0.90	166	20	2.0	
			15	I	0.10	...	70	...	...	
			15	I	0.07	0.26	365	28	3.1	
			16	I	0.08	...	186	...	...	
J. M.....	21	F	15	I	0.03	2.65	220	18	0.5	
			16	I	0.03	...	430	...	...	
			21	I	0.014	0.38	670	20	2.0	
			17	I	0.33	0.85	120	18	1.5	
J. B.....	29	M	19	I	0.18	...	194	...	...	
			19	I	0.22	1.14	160	26	0.4	
			19	I	0.38	...	173	...	...	
			21	I	0.11	0.94	486	42	2.5	
J. H.....	30	M	21	I	0.18	...	380	...	...	
			25	I	0.28	0.62	192	40	2.4	
			23	I	0.09	0.44	280	26	1.5	
			25	I	0.90	...	98	...	...	
P. R.....	28	M	23	I	0.37	0.47	133	20	2.4	
			25	I	0.10	...	230	...	...	
			10	P	0.25	0.60	53	24	1.3	
			12	I	0.06	...	200	...	...	
G. P.....	32	F	10	P	0.04	0.87	120	24	1.0	
			12	I	0.09	...	280	...	...	
			16	I	0.02	0.63	600	30	2.0	
			16	P	0.13	0.88	346	24	1.6	
U. S.....	31	M	8	I	0.01	...	333	24	...	
			16	P	0.50	...	193	...	...	
			16	I	0.13	0.88	280	...	...	
			16	I	0.60	...	96	...	...	
E. G.....	28	F	8	I	0.07	0.71	160	28	1.6	
			10	P	0.10	...	96	...	...	
			14	I	0.33	0.55	260	28	3.0	
			14	I	0.33	...	183	...	...	
			14	I	0.14	0.50	180	34	2.4	
			14	I	0.10	...	310	...	...	

\* Inside diameter.

† Profuse.

‡ Intermittent.

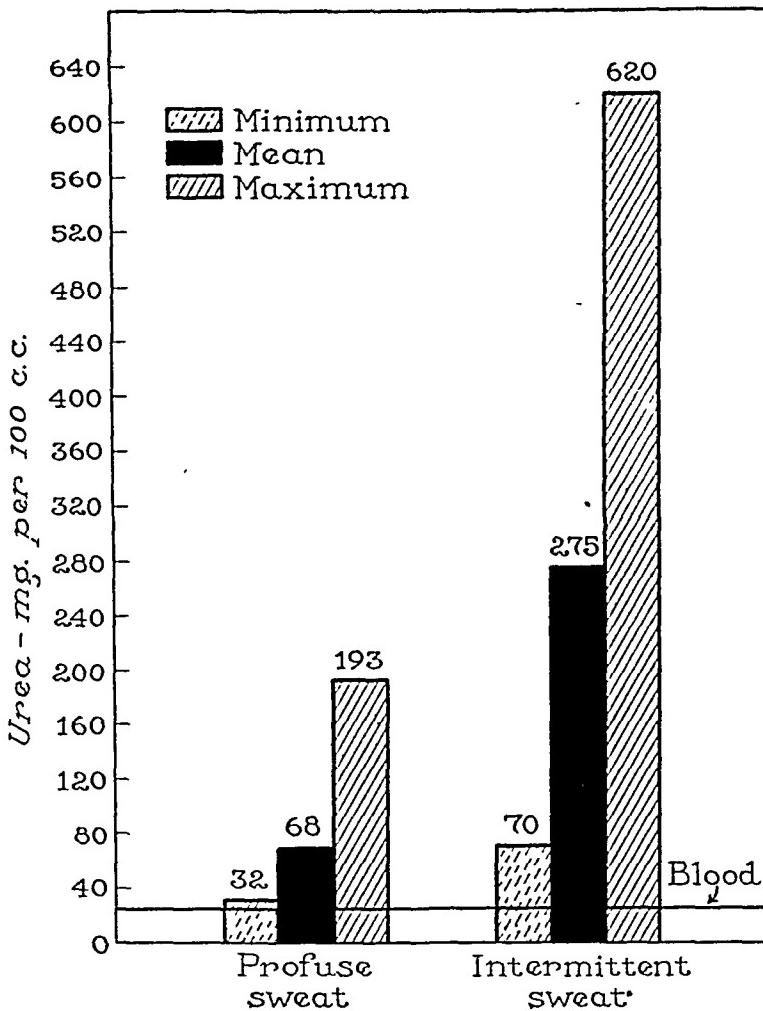


Fig. 2.—The mean values of urea (expressed as mg. urea per hundred cubic centimeters of sweat) with minimum and maximum for the two physiologic types of sweating and mean value for blood urea in all types.

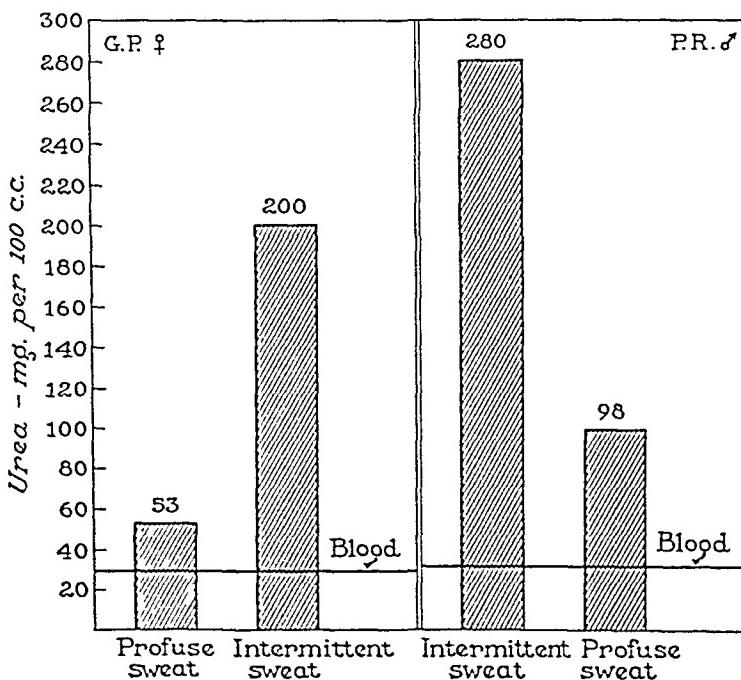


Fig. 3.—Two examples of the physiologic types of palmar sweat delivered on request in the same half-hour period by the same person. G.P. (♀) delivered her types of sweat in the reverse order from that requested from P. R. (♂).

Intermittent sweat (fig. 2) was collected a total of fifty times from 8 men and 11 women. Here the average value for urea in the sweat was 275 mg. per hundred cubic centimeters (minimum 70 and maximum 620 mg. urea per hundred cubic centimeters of sweat). The sweat gland, therefore, when working intermittently is able to concentrate urea to an extent even greater than when working continuously. The value of urea in the urine averaged 1.5 Gm. per hundred cubic centimeters and bore no relation to the concentration of urea in the palmar

TABLE 2.—*Values for Urea in Sweat, Blood and Urine Before and After Oral Administration of Urea*

Subject	Age, Years	Sex	Sweat Volume,*							
			Time as Min.		Mm. I.D.†	Sweat Tube per Minute	Blood		Urine	
			After Oral Adminis- tration of Urea	in 0.35			Mg. per 50 Glands	Mg. per 100 Cc.	Volume, Cc. per Minute,	Urea, Gm. per Output
Fasting Levels										
D. M.....	22	F	..	..	0.47 0.48	34 51	26	0.66	1.29	2.54
					30 Gm. Urea (10 per Cent Solution)					
			1	0	...	332	0.71	2.12	2.54	
			1	10	0.40	277	..	....	....	
			1	25	0.46	207	..	....	....	
			1	40	...	..	112	2.30	3.59	3.70
			23	25	0.65	72	..	....	....	
			23	40	0.80	75	28	0.40	3.04	0.43
Fasting Levels										
R. C.....	24	F	..	..	0.47 0.48	38 47	16	0.30	1.87	0.12
					16 Gm. Urea (10 per Cent Solution)					
			1	0	...	..	0.62	3.18	1.49	
			1	10	1.60	88	60	....	....	
			1	35	1.20	77	58	....	....	
			1	40	...	..	..	0.09	3.35	0.12
Fasting Levels										
D. M.....	22	F	..	..	0.62	54	24	0.20	2.67	0.19
					20 Gm. Urea (10 per Cent Solution)					
			0	50	...	..	0.33	4.03	0.73	
			1	0	0.45	131	68	....	....	
			1	30	0.45	146	78	....	....	
			1	35	...	..	..	1.20	4.87	2.29

\* All specimens of sweat were of the so-called profuse physiologic type.

† Inside diameter.

sweat. The average value for urea in the blood was 25 mg. per hundred cubic centimeters (minimum 14, maximum 42 mg. urea per hundred cubic centimeters of blood).

In seven instances we were able to collect on request the two different physiologic types of sweat in the same half-hour period from the same subject. Figure 3 illustrates two such collections. The concentration of urea in the intermittent type of sweat was always higher than in the profuse type of sweat, regardless of which type was delivered first in the thirty minute period.

To study the effect of elevated levels of urea in the blood on the palmar sweat of normal subjects we fed urea by mouth three times to persons (2 women, R. C. and D. M. [table 1]) who were known to be able to excrete profuse continuous sweat. All specimens of sweat collected were of this profuse type. Specimens of blood and urine were also collected for study. The results are shown in table 2. The level of urea in the sweat paralleled the rise and fall of urea in the blood, keeping above the level of urea in the blood at all times.

#### SUMMARY

Seventy-seven specimens of palmar sweat, collected for the study of urea, were grouped into two physiologic types: (1) profuse and (2) intermittent. Seven subjects were able to deliver both profuse and intermittent types of palmar sweat on request, for collection within a half-hour period. The profuse type of palmar sweat had a lower concentration of urea (mean, 68 mg. urea per hundred cubic centimeters) than the intermittent type of palmar sweat (mean, 275 mg. urea per hundred cubic centimeters). In both types, however, the concentration of urea was higher than the level of urea in the blood, but not as high as the level of urea in the urine.

On the three occasions when urea was fed by mouth to normal subjects delivering profuse palmar sweat, the level of urea in the sweat paralleled, but always exceeded, the rise and fall of urea in the blood.

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# EXTENSIVE TRICHOPHYTON PURPUREUM INFECTION, WITH NEVOID ANOMALY OF THE SKIN

Report of a Case, Together with Mycologic and Physiologic Studies

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LOCALIZED dermatomycosis involving limited areas of the skin, especially of the feet, is one of the commonest cutaneous diseases. Statistics indicate that in the United States the incidence of fungous infections of the feet in large cities reaches 30 to 90 per cent of the adult population, with a higher incidence in the southern than in the northern part of the country. In spite of this high incidence, cases of more generalized dermatomycoses, affecting large areas of the skin of the trunk and of the extremities, are relatively rare. In general the widespread eruptions are caused by the same species of fungi which are responsible for the more localized forms. Unusually extensive involvement of the skin may be due to several factors, which may include either an exceptional vitality and pathogenicity of a particular strain of fungus or an abnormality of the skin itself which makes it an especially favorable substrate for propagation of the parasites. Among several species of fungi which are capable of producing generalized dermatomycoses *Trichophyton purpureum* occupies an important place, at least in this country.

Thus Lewis and Hopper<sup>1</sup> stated that *T. purpureum* is one of the fungi which cause lesions involving large surfaces of skin of the trunk and of the extremities, at times of a bizarre and configurate type or resembling psoriasis or even simulating *tinea imbricata*.

Lewis, Montgomery and Hopper<sup>2</sup> observed 3 instances of eruptions caused by *T. purpureum* and involving large areas of the skin of the trunk. One of these patients presented large circinate plaques on the

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This case was presented by the authors on May 2, 1946 before the Section of Dermatology and Syphilology of the New York Academy of Medicine.

1. Lewis, G. M., and Hopper, M. E.: An Introduction to Medical Mycology, ed. 2, Chicago, The Year Book Publishers, Inc., 1943, pp. 76 and 79.

2. Lewis, G. M.; Montgomery, R. M., and Hopper, M. E.: Cutaneous Manifestations of *Trichophyton Purpureum* (Bang), Arch. Dermat. & Syph. 37:823 (May) 1938.

chest, the left shoulder and the back. On the left hand and the fingers there were erythematous squamous and papular lesions. Circinate patches were also present on the left wrist. The skin of the left palm was thickened and scaly. Both soles were erythematous, thickened and scaly. Scaly patches were present on the dorsum of the foot. The authors stated that the lesions of the glabrous skin should be differentiated from atypical psoriasis, neurodermatitis and erythema annulare centrifugum. The lesions on the hands and feet may also simulate eczema, calluses and arsenical keratoses.

One of us<sup>3</sup> described 2 cases of generalized infection of the skin by *T. purpureum*. One patient presented erythematous squamous patches of various sizes on the abdomen, groins and lower extremities. In another patient an eruption of the same type involved large areas on the trunk and upper and lower extremities, including the palms and the soles. All finger nails and all but two toe nails were also affected.

Tolmach and Schweig<sup>4</sup> described a case of *T. purpureum* infection involving almost two thirds of the entire skin. There were large sharply marginated patches, with serpiginous bizarre contours. The unusual feature of this case was the presence of vesicular and papulovesicular lesions, which suggested dermatitis herpetiformis. This clinical diagnosis had been made by a number of competent dermatologists before the mycologic studies established the fungous causation of the disease.

Lewis<sup>5</sup> presented a patient with lesions on the feet, various parts of the body, scalp and beard. *T. purpureum* was cultured from several areas, including the scalp and beard.

Ayres<sup>6</sup> presented a patient with erythematous scaly lesions on the face, ears, feet, ankles and buttocks. A number of toe nails were also affected. *T. purpureum* was cultured from several areas. This patient also had lesions on the mucous membrane of the mouth, from which *Monilia albicans* was recoverable in cultures.

There are two reports which are of particular interest in connection with the case described in the present communication: Lane<sup>7</sup> presented a patient who had generalized ichthyosis since birth and whose fungous eruption on the chest, back, buttocks and thighs consisted of foci with

3. Muskatblit, E.: Observations on *Epidermophyton Rubrum* or *Trichophyton Purpureum*, *Mycologia* **25**:109 (March-April) 1933.

4. Tolmach, J. A., and Schweig, J.: Generalized *Trichophyton Purpureum* Infection Simulating Dermatitis Herpetiformis, *Arch. Dermat. & Syph.* **41**:732 (April) 1940.

5. Lewis, G. M.: Dermatophytosis, *Tinea Barbae* and *Tinea Corporis* Due to *Trichophyton Purpureum*, *Arch. Dermat. & Syph.* **41**:938 (May) 1940.

6. Ayres, S., Jr.: Dermatophytosis Due to *Trichophyton Purpureum* with *Monilia* Infection of the Mouth, *Arch. Dermat. & Syph.* **51**:285 (April) 1945.

7. Lane, C. G.: *Tinea Corporis* (*Trichophyton Purpureum*); *Moniliasis* of Feet; Ichthyosis, *Arch. Dermat. & Syph.* **40**:119 (July) 1939.

red raised borders, forming geometric and polycyclic patches. Cultures of material from the body showed *T. purpureum*. The interdigital webs of the feet were macerated, and *M. albicans* was cultured from there. Swartz and Conant<sup>8</sup> observed 4 cases of extensive lichenified eruption caused by *T. purpureum*. One of the patients, who also had ichthyosis, had papular lichenified lesions on the upper and lower extremities, the lower part of the trunk, the chest and the suprapubic area. The toe nails of the right foot were also affected and were discolored and deformed. The other patients presented circular and gyrate lesions, with lichenified papular borders and also lichenified plaques of various sizes over the legs, arms and trunk.

#### REPORT OF A CASE

A. R., a white man aged 24, when first seen on June 19, 1945 in the private practice of Dr. Marion B. Sulzberger and one of us (R.L.B.), stated that he had an eruption on both palms and soles since birth and an eruption on the body and other parts of the extremities since the age of 13 or 14.

The patient's parents were not related; his only sister had no cutaneous abnormalities, and there was no other family history of cutaneous diseases.

In 1937 the patient was hospitalized at the Beth Israel Hospital in Boston, and the diagnosis of acanthosis nigricans was made. There were dryness and cracking of the nails in addition to an eruption on the feet, hands, abdomen, thighs and back. No examination for fungi was carried out at that time.

In December 1943 the patient was seen at the New York Skin and Cancer Unit, where a clinical and histologic (biopsy specimen was taken from the back) diagnosis of erythroderma ichthyosiforme congenitum was made. The patient was presented<sup>9</sup> at the New York Academy of Medicine under this diagnosis, which was accepted by those present.

When first seen by us in June 1945, A. R. presented the following cutaneous changes: There was an extensive generalized somewhat erythroderma-like eruption, covering the hands (fig. 1), forearms, arms, feet, legs, thighs, neck, chest, back and abdomen (fig. 2). The lesions on the arms and legs consisted of large gyrate and circinate slightly scaly areas which were brownish, infiltrated and lichenified, with well defined and raised borders. These lesions somewhat resembled a relief map, and the intervening skin appeared normal. The patient stated that the shapes of these lesions changed gradually in that previously unaffected areas became affected and vice versa.

The neck presented well defined, but only slightly elevated, erythematous and scaly circinate patches. The trunk was the site of diffuse scaling, dryness, thickening and yellowish brown to brownish red discoloration in large areas. Some of the borders of these large areas were also well defined.

On the palms and soles there was decided hyperkeratosis, with some heaping and fissuring of horny material. All the finger nails and toe nails were yellowish, brittle, fissured and misshapen. The nails had been filed down by the patient, as

8. Swartz, J. H., and Conant, N. F.: Extensive Lichenified Eruption Caused by Trichophyton Rubrum, Arch. Dermat. & Syph. 42:614 (Oct.) 1940.

9. Rosen, I.: Erythroderma Ichthyosiforme Congenitale, Arch. Dermat. & Syph. 51:161 (Feb.) 1945.

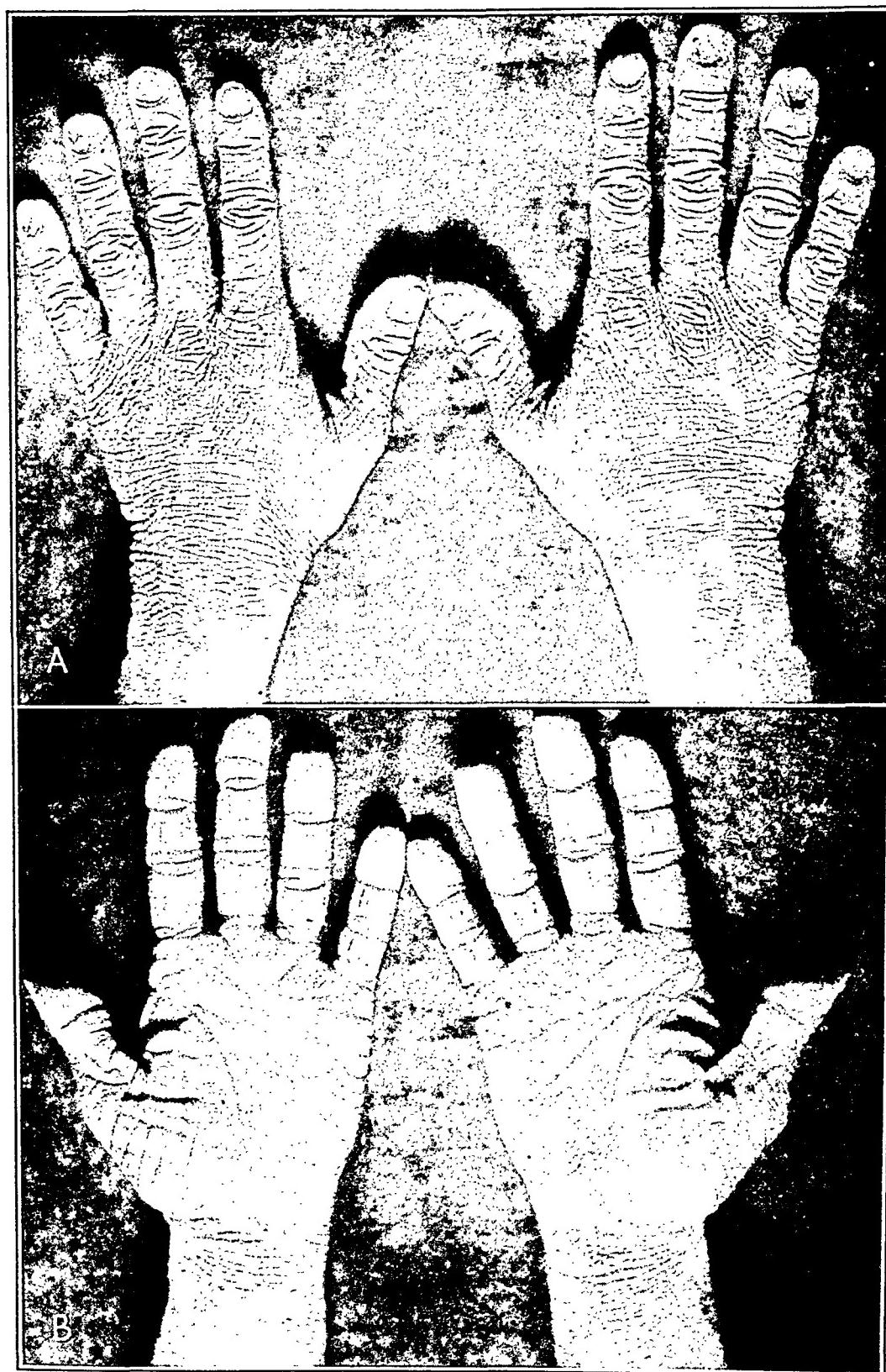


Fig. 1.—A, dorsa of the hands, showing thickening, lichenification and scaling. The nails are almost spoon shaped because of their having been filed down by the patient. B, palms, showing hyperkeratosis and scaling. On the right wrist fairly well defined borders of scaly hyperpigmented patches are seen.

failure to do so always resulted in a heaped-up nail which interfered with his activities.

Because of the well defined borders of parts of the eruption and the presence of circinate patches, scrapings from different areas of the body were taken for microscopic and cultural examination for fungi. Characteristic fungous mycelia were microscopically seen in specimens from the chest, shoulder, arm, neck and center of the back.

On Sabouraud's dextrose peptone agar the culture obtained from the scrapings from the neck was white, downy and hemispheric in shape. It grew side by side with saprophytes, and in order to save the strain for further study three transfers into a fresh tube were made. The three colonies which developed after six weeks of growth were of different configuration (fig. 3). The uppermost culture, growing on a thin layer of the medium, had a heaped-up center sur-



Fig. 2.—*A*, severe generalized involvement of the front of the body, with circinate, gyrate and polycyclic lesions. *B*, diffuse erythema and scaling over the upper part of the back and buttocks; circinate and gyrate lesions of the middle and lower parts of the back.

rounded by a wide flat zone. The middle colony showed a well formed crater in the center, with a depression and an elevated wall around it. The colony at the bottom of the tube, growing on a heavier layer of the medium, was cerebriform, with numerous grooves and rounded convolutions. The surface was velvety and like a fine powder. The color was white with a faint rose tinge. The back surface showed red pigmentation, especially noticeable under the edge of the colony near the wall of the tube. A single point transfer into a fresh tube developed the same morphologic picture.

Culture mounts made in lactose phenol blue (fig. 4 and 5) revealed a mass of septate and branched hyphae, a moderate number of small spores (microconidia) and a great number of macroconidia. The latter were of a tapering type, long,

finger-like, more cylindric than fusiform, with thin and smooth walls and numerous cross walls dividing them into several compartments. This species was identified as *T. purpureum*.

The patient was seen again December 14, when seven separate specimens of scrapings were taken from different lesions, namely, the wrists, palms, thighs, toes, soles, finger nails and toe nails. All the specimens which were examined microscopically in potassium hydroxide showed the presence of fungi in the form of long septate and branched filaments (fig. 6). Material from the same seven specimens of scrapings were planted on Sabouraud's medium, three tubes for each specimen. In spite of the large amount of material used, it proved impossible to

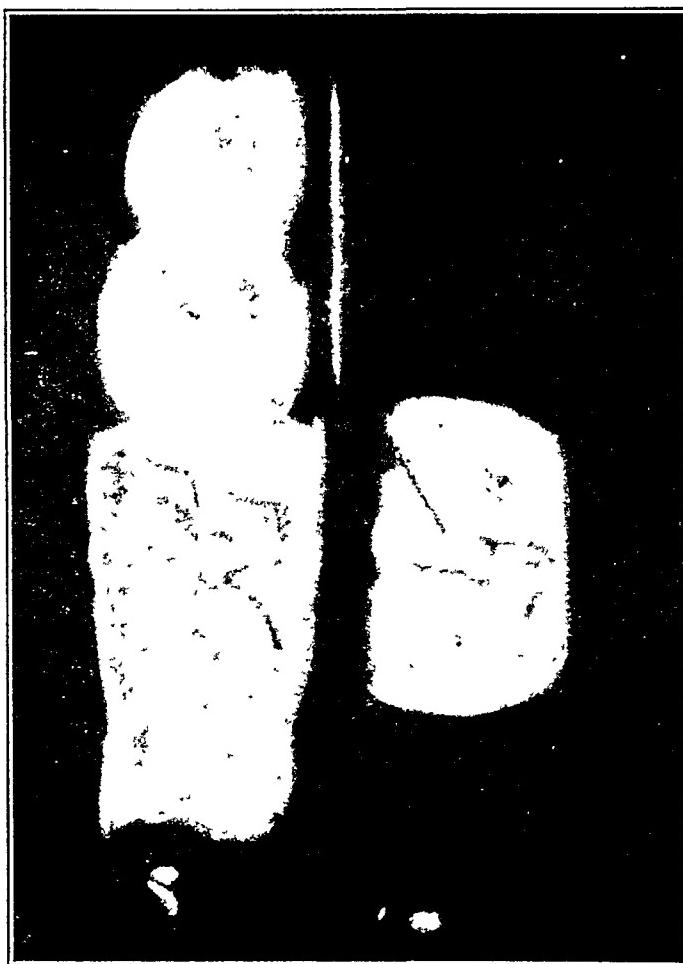


Fig. 3.—Cultures from the neck on Sabouraud's dextrose peptone agar, showing *T. purpureum*. Left, six weeks old and right, three weeks old.

isolate the pathogenic fungus because of an abundant growth of various saprophytes in all tubes.

After the diagnosis of generalized dermatomycosis due to *T. purpureum* had been made, the patient was given various forms of local treatment, none of which was used more than once or twice because the patient objected to the physical properties or the odor of the preparations.

On Jan. 21, 1946 the patient was given an oil in water emulsion cream<sup>10</sup> which contained coal tar, sulfur and salicylic acid.

10. "Pragmatar" (Smith, Kline & French Laboratories).

After an absence of almost three months he was again seen on April 11. The eruption on his body had cleared with the following exceptions: There was still thickening of the dorsa of the fingers and to a slight degree of the dorsa of the

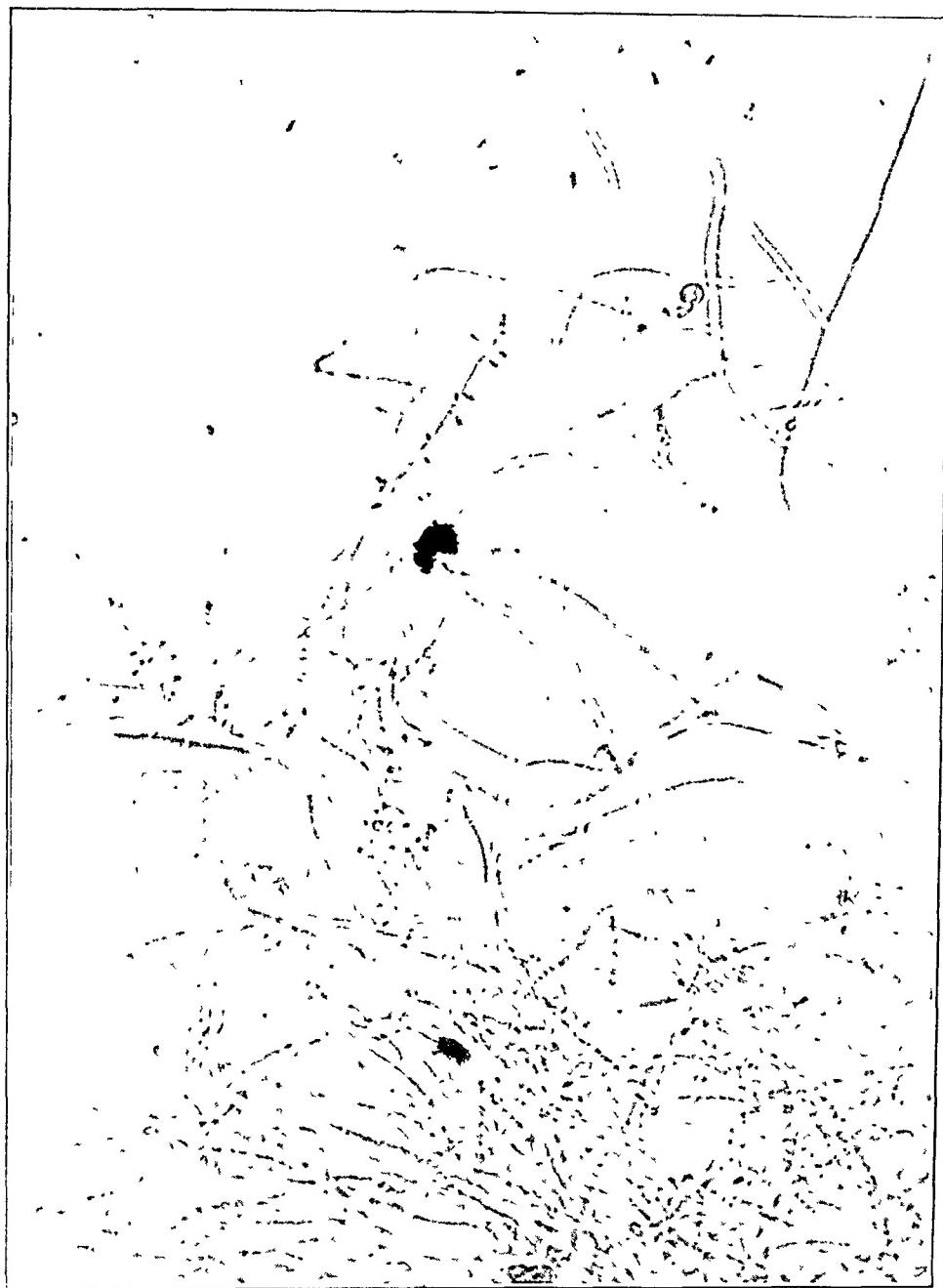


Fig. 4.—Culture mount of *T. purpureum* in lactose phenol blue, showing mycelium with microconidia.  $\times$  approximately 479.

metacarpal area and the wrists. The finger nails were dry, brittle, slightly yellowish and fissured; they had been shaved down with a razor blade. On the palms there was hyperkeratosis extending to the wrists. On the legs there were lichenified, thickened, brownish, slightly scaly and hyperkeratotic well defined

patches, of various shapes and sizes. There was hyperkeratosis of the heels. The soles were greatly hyperkeratotic and thickened, with formation of deep clefts in the hyperkeratotic areas. The toe nails were yellowish and onychogrypotic. Microscopic examination of scrapings taken on May 10 from the palms and fingers,



Fig. 5.—Culture mount of *T. purpureum* in lactose phenol blue, showing multi-septate macroconidia.  $\times$  approximately 468.

two finger nails, the right sole and one toe nail showed again fungous mycelia. No mycelia were found in material from one of the hyperkeratotic patches on the

legs. On Sabouraud's medium cultures of material from the same areas failed to show any growth of pathogenic fungi.

Dr. Wilbert Sachs, of the New York Skin and Cancer Unit, reviewed the sections of the biopsy specimen taken from the back in 1944 and reported an

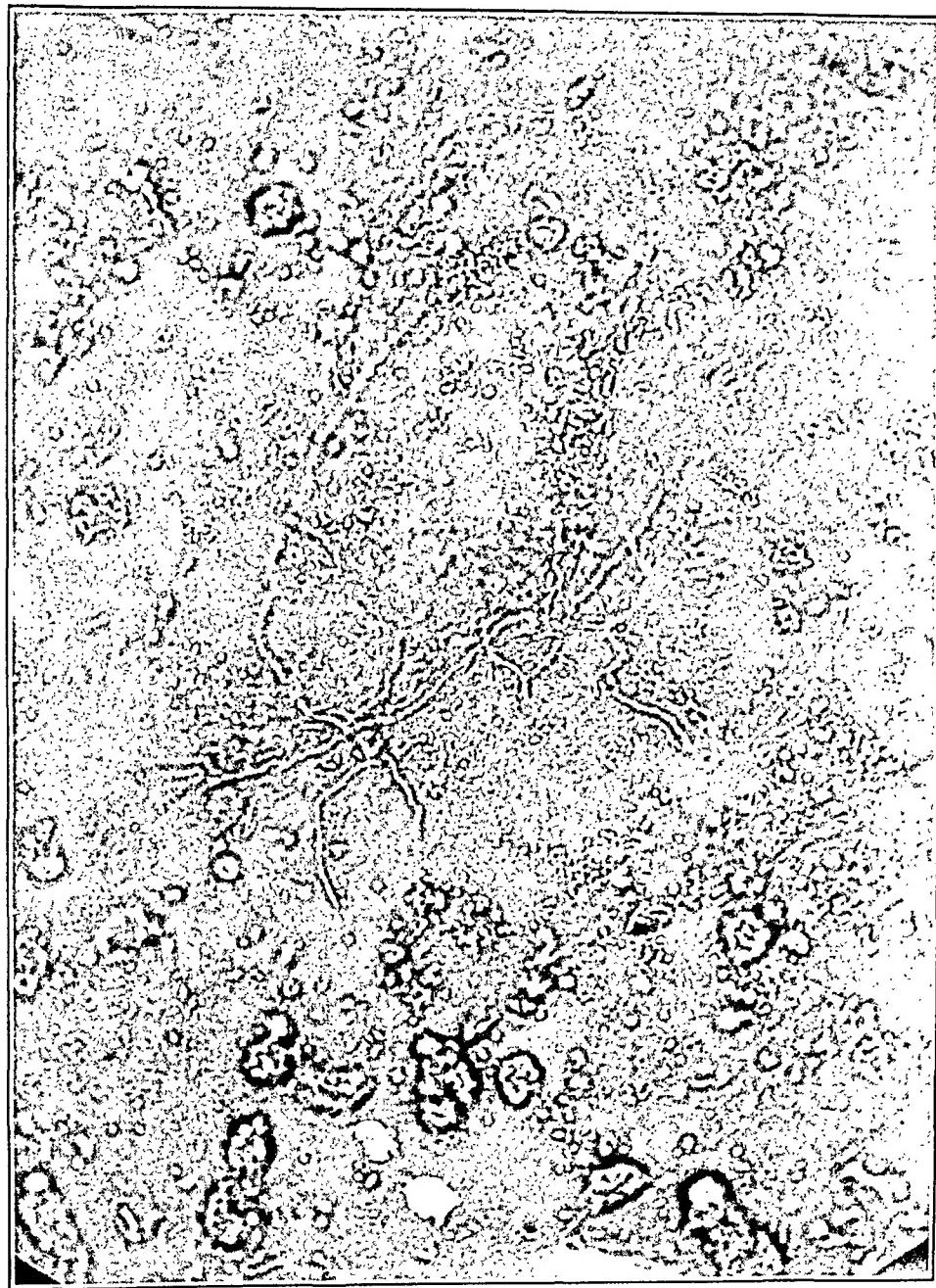


Fig. 6.—Fungi in scrapings from the finger nails (potassium hydroxide preparation).  $\times$  approximately 492.

ichthyosiform type of process on the basis of the following observations: The epidermis was irregularly acanthotic. The surface was verrucous and covered

with a densely laminated horny layer. The granular layer was present throughout. The palisade layer was intact, and no important changes were seen within the epidermis. The vessels of the upper layer of the cutis were dilated, and about them was a pronounced reaction involving small round cells, wandering connective tissue and plasma cells. There was a similar reaction about all sweat ducts. No mycelia were seen in the horny layer. There was a moderate amount of interstitial edema in the cutis.

*Sweat Production.*—When first seen A. R. stated that he did not perspire at all except on the neck, face and scalp. For years he had often felt "extremely hot" because of his inability to sweat on the body. As he is a saxophone player who frequently has to work in overheated rooms, the inability to perspire caused a great deal of discomfort during all seasons of the year. When A. R. was seen again in April 1946, after the rash on his body had cleared, he remarked that for the first time he was perspiring on the body.

Studies on the quantitative output of water through the sweat of A. R. were carried out on May 9 by Dr. Franz Herrmann of the New York Skin and Cancer Unit. These studies, in which a fluorescence method was used,<sup>11</sup> showed that, except on the face, A. R. had an abnormally low production of sweat, i.e., almost a complete absence of sweat when he was at rest with "normal" room temperature. However, after insertion of one arm into a heating device at 85 C. (185 F.) for thirty minutes, there was, in general, only slightly less sweating on the body than in normal persons.

*pH of the Skin.*—On Dec. 13, 1945, while A. R. still had his generalized eruption, determinations of the  $p_{H}$  were made on twenty-two affected and unaffected areas of the skin. The method of Bernstein and Herrmann<sup>12</sup> was used. The values for the  $p_{H}$  of the face and retroauricular areas were 4.2, 4.3 and 4.5, while the values on the rest of the body were between 4.3 and 6.5, with an average value of 5.5. No significant differences were found between affected and unaffected cutaneous areas on the body.

Twelve additional determinations of  $p_{H}$  were done by Dr. Franz Herrmann on May 9, 1946, at a time when the eruption on the patient's body had cleared except for the areas aforementioned. The  $p_{H}$  on the forehead was 4.9. The values on the rest of the body were between 3.7 and 5.6, with an average value of 4.3.

#### COMMENT

This case of generalized dermatomycosis is of interest not only because of its unusual extent but because of the cutaneous changes which probably preceded and which were associated with the fungous infection. It appears probable that the diagnosis of erythroderma ichthyosiforme congenitum which had been made in 1944<sup>9</sup> was incorrect. However, there is little doubt that this patient had a nevoid anomaly of the skin. The evidence in favor of such an anomaly can be summarized as follows: (1) the presence of palmar and plantar hyperkeratosis since birth; (2) decided changes in the finger nails and toe nails, including definite onychogryposis of the toe nails (could have been due to fungous infec-

11. Hand, W. C.: Personal communication to the authors.

12. Bernstein, E. T., and Herrmann, F.: The Acidity on the Surface of the Skin, New York State J. Med. 42:436 (March 1) 1942.

tion), (3) the presence on the legs of a few patches which, as far as could be ascertained, were free from fungous infection, and the appearance and persistence of which suggested a nevoid character, (4) nevoid changes in skin from the back on histologic examination in 1944, (5) the absence of sweating on the body and the symptoms of anhidrosis, as described by the patient, up to the time of clearing of the body eruption in 1946 (could have been due to fungous infection) and (6) the abnormally low output of sweat on the body at normal temperatures when the patient was at rest and the somewhat low output of sweat on the body with deliberate stimulation of sweating through exposure to heat, as was demonstrated in laboratory tests after the eruption on the body had cleared.

The previously reported cases of generalized *T. purpureum* infections in patients with ichthyosis<sup>13</sup> and the findings in our patient A. R. suggest that the susceptibility to fungous infection and the severe generalization and persistence of the infection may in these patients have been due to the underlying nevoid anomaly of the skin. In our patient this congenital anomaly probably furnished an excess of horny tissue and thus a fertile soil for the growth of the fungi and may have led to a lack of fungicidal substances, in particular fatty acids,<sup>14</sup> because of the relative or complete absence of sweat on the body. The theory that all the changes in this patient were caused by a fungous infection during early childhood has been suggested,<sup>15</sup> but only as a remote and unlikely possibility.

We should like to call particular attention to the relative ease with which the fungous infection on the body cleared under treatment, once a remedy had been found that the patient was willing to use. This point is of particular interest in connection with the recent discussions on the relative resistance and lack of resistance, respectively, to treatment of fungous infection due to *T. purpureum*.<sup>16</sup> Another point of interest is the fall in the  $p_H$  of the skin of the body subsequent to the clearing of the eruption on the body and the clinically noticeable appearance of sweat on the body. The average  $p_H$  of the body fell from 5.5 to 4.3, while there was no significant change in the  $p_H$  of the face, which apparently had always had a quantitatively normal secretion of sweat.

13. Lane.<sup>7</sup> Swartz and Conant.<sup>8</sup>

14. Peck, S. M., and Rosenfeld, H.: The Effects of Hydrogen Ion Concentration, Fatty Acids and Vitamin C on the Growth of Fungi, *J. Invest. Dermat.* **1**:237 (Aug.) 1938; correction, *ibid.* **1**:398a (Oct.) 1938.

15. Sulzberger, M. B.: Personal communication to the authors.

16. Lewis and Hopper.<sup>1</sup> Weidman, F. D., and Glass, F. A.: Dermatophytosis and Other Forms of Intertriginous Dermatitis of the Feet: A Comparison of Therapeutic Methods, *Arch. Dermat. & Syph.* **53**:213 (March) 1946.

## SUMMARY

A case is reported of a nevoid anomaly of the skin, associated with a generalized and unusually extensive fungous infection due to *T. purpureum*. It is suggested that the nevoid anomaly of the skin, leading to an excess of horny tissue (including keratosis palmaris et plantaris) and to a relative lack of sweat, may have been a factor in making this patient's skin unusually susceptible to the fungous infection. It is pointed out that such factors may be operable in other severe, extensive or otherwise unusual fungous infections. The ready response to simple external treatment supports the concept that *T. purpureum* infections are not necessarily always refractory to local treatment.

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## KAPOSI'S VARICELLIFORM ERUPTION

Isolation of the Virus of Herpes Simplex from the Cutaneous Lesions  
of Three Adults and One Infant

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AND

KATHARINE DODD, M.D.

CINCINNATI

TOWARD the end of the last century Kaposi<sup>1</sup> described a syndrome in children. The young patients experienced an eruption and a febrile reaction as a complication of preexisting atopic dermatitis. Lesions usually appeared over the old atopic dermatitis, but occasionally invaded the neighboring healthy skin. The lesions went through various stages of vesiculation, umbilication, desiccation and rupture. The acute lesions appeared in recurrent crops for many days, and when they finally healed only signs of the original atopic dermatitis persisted. No mention was made in the original description of lymph node involvement, which was a common observation in subsequent reports of similar cases. Shortly thereafter, under the title of "Pustulosis acuta varioliformis," Juliusberg<sup>2</sup> described a fatal case in which there were lesions similar to those of Kaposi's varicelliform eruption. A similar disease picture has been described by many authors under the name of eczema vaccinatum. Many of these persons had been exposed to a recently vaccinated member of the family or had themselves been recently vaccinated. Vaccine virus was recovered<sup>3</sup> or Guarnieri bodies were demonstrated<sup>4</sup> from the cutaneous lesions of several patients with an eruption

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From the Children's Hospital Research Foundation and the Departments of Pediatrics, Bacteriology and Dermatology and Syphilology of the University of Cincinnati College of Medicine.

1. Kaposi, M.: Pathology and Treatment of Diseases of the Skin, New York, William Wood & Company, 1895, p. 346.

2. Juliusberg, F.: Ueber Pustulosis acuta varioliformis, Arch. f. Dermat. u. Syph. **46**:21, 1898.

3. Hershey, F. B., and Smith, W. E.: Generalized Vaccinia in an Eczematous Child, Am. J. Dis. Child. **69**:33 (Jan.) 1945.

4. Freund, H.: Zur Aetiologie der pustulosis vacciniformis acuta (Kaposi-Juliusberg), Dermat. Wchnschr. **98**:52 (Jan.) 1934. Ellis, F. A.: Eczema Vaccinatum: Its Relation to Generalized Vaccinia; Report of Two Cases, J.A.M.A. **104**:1891 (May 25) 1935. Pepple, A. W.; Murrell, T. W., and Fowlkes, R. W.: The Varicelliform Eruption of Kaposi, South. M. J. **35**:667 (July) 1942.

resembling that described by Kaposi. Recently the virus of herpes simplex has been isolated from several patients presenting the syndrome,<sup>5</sup> and it is now thought that there are at least two similar eruptions which occur on eczematous lesions—one caused by the virus of vaccinia and known as eczema vaccinatum and the other caused by the virus of herpes simplex and known as Kaposi's varicelliform eruption.

Of 96 cases of Kaposi's varicelliform eruption recorded in the literature 75 occurred in children and only 21 in adults. Of the patients whose exact age was recorded, 24 or 32 per cent were infants in the first year of life. The death rate was 23 per cent in infants and 9 per cent in adults. It seems probable that this is a higher death rate than actually obtains, as many milder cases probably were not recorded.

The following report is of 4 cases of Kaposi's varicelliform eruption, all of which were seen within a short period of time. The fact that 3 of the patients were adults appears of importance, as the disease is apparently much less common in adults than in children and the causative agent has been isolated from the lesions of adults only twice.<sup>6</sup> All 4 patients gave a history of definite exposure to the virus of herpes simplex. Strains of herpes simplex were isolated from the cutaneous lesions of all.

#### REPORT OF CASES

CASE 1.—J. M., a 14 month old white boy, was admitted to The Children's Hospital Nov. 26, 1945, because of infected atopic dermatitis. The patient had had atopic dermatitis since 1 month of age and had been admitted to the hospital with the same complaint in April 1945. There was a familial history of atopy. The child had not been vaccinated, nor was there any history of recent exposure to vaccine virus. However, the mother had had "fever blisters" less than a week before the child's admission. The child's temperature on admission was 103.4 F. He was acutely ill and irritable. The skin of the face and neck was red and scaling, and over a large area of the face the lesions were secondarily infected and crusted. There were large fluctuant lymph nodes behind the right ear. Chronic eczematoid lesions appeared around the hands, popliteal and cubital spaces. The trunk was relatively free of lesions, but the skin was dry, scaly and excoriated. The tonsils were enlarged and the pharynx injected. There was slight edema of the feet. The patient was given penicillin intramuscularly. Two days after admission a post-

5. (a) Wenner, H. A.: Complications of Infantile Eczema Caused by the Virus of Herpes Simplex, *Am. J. Dis. Child.* **67**:247 (April) 1944. (b) Barton, R. L., and Brunsting, L. A.: Kaposi's Varicelliform Eruption: Review of the Literature and Report of Two Cases of Its Occurrence in Adults, *Arch. Dermat. & Syph.* **50**:99 (Aug.) 1944. (c) Blattner, R. J.; Heys, F. M., and Harrison, M. L. K.: Etiology of Kaposi's Varicelliform Eruption, *J. Pediat.* **27**:207 (Sept.) 1945. (d) Lynch, F. W.; Evans, C. A.; Bolin, V. S., and Steves, R. J.: Kaposi's Varicelliform Eruption: Extensive Herpes Simplex as a Complication of Eczema, *Arch. Dermat. & Syph.* **51**:129 (Feb.) 1945. (e) Jaquette, W. A.; Convey, J. H., and Pillsbury, D. M.: Kaposi's Varicelliform Eruption: Studies on Etiology, *Am. J. Dis. Child.* **71**:45 (Jan.) 1946.

6. Barton and Brunsting.<sup>5b</sup> Lynch, Evans, Bolin and Steves.<sup>5d</sup>

auricular abscess on the right side was drained. At the same time a varicelliform eruption developed on the face and nose, with some scattered lesions over the rest of the body. The lesions were discrete, umbilicated and superimposed on the eczematized area. Herpetic lesions were noted on the inner surface of the lips and gums. A diagnosis of Kaposi's varicelliform eruption was made<sup>7</sup>. The temperature rose to 105.0 F. and remained elevated until December 3, when it dropped to normal and then rose to 102.5 F. on December 7 and remained above 100 F. until December 11, at which time penicillin therapy was discontinued. A transfusion of 150 cc.



Fig. 1—Kaposi's varicelliform eruption (case 1).

of whole blood was given. The temperature remained elevated, and on December 13 it rose again to 102.0 F. Penicillin was given for four more days, and penicillin ointment was used on the skin. Sulfadiazine was also used. Because it was thought that the fever might be due to the extensive involvement of the skin, with interference with the sweating mechanism, the patient was placed in a cool quiet room. The temperature dropped dramatically to normal and remained normal until the time of discharge on the thirty-eighth day of hospitalization. At this time the herpetic lesions were almost entirely healed, but the atopic dermatitis remained. Culture of the auricular abscess on November 28 revealed a pure culture of hemolytic streptococcus. The blood culture was sterile on December 2. The urine was

7. Diagnosis was made by Dr. Leon A. Goldman of the Department of Dermatology and Syphilology.

essentially normal. Leukocyte counts ranged between 9,800 and 11,200. The differential counts were not remarkable. The hemoglobin varied from 8.7 to 13.6 Gm. and the erythrocytes from 3,600,000 to 4,500,000. The albumin-globulin ratio was 3.4 to 3.0. Crusts and vesicular exudate obtained from lesions on the face on November 29 were applied to the scarified corneas of a rabbit. Keratoconjunctivitis developed in both eyes.

**CASE 2.**—F. R., a white boy aged 16, had had atopic dermatitis of varying severity since infancy. For three or four months previous to the present episode the face, ears, neck and cubital spaces had presented only a dry scaling eczematoid eruption. Four days previous to admission to Christ Hospital he experienced acute dermatitis superimposed on all the eczematized areas. On examination numerous lentil-sized umbilicated vesicles and pustules surrounded by red halos were seen. These were closely set over the face and neck and grouped on the arms and chest, with discrete lesions scattered over the trunk. The lesions and were in many areas ruptured. These areas were oozing and crusted. There was edema of the eyelids, face and neck. There was decided cervical lymphadenopathy. The temperature on admission was 102.0 F. The leukocytes numbered 16,000, erythrocytes 4 per cent and mononuclear cells 3 per cent. The hemoglobin measured 13.5 Gm. Cultures of the urine and blood were sterile. A culture of the lesions revealed coccus. An agent capable of provoking keratoconjunctivitis in rabbits was obtained from the early cutaneous lesions. The patient's temperature rose rapidly to 105.0 F. He became irrational and at intervals drowsy. Penicillin was administered parenterally and topically, without apparent effect. He was given 1 unit of pooled plasma on two occasions forty-eight hours apart, with no apparent benefit. Two intravenous infusions of 1,000 cc. of 5 per cent solution of dextrose in isotonic solution of sodium chloride with 10 grains (0.65 Gm.) of acetylsalicylic acid apparently reduced the isolated lesions temporarily. After five days the isolated lesions became crusted, new lesions ceased forming, the swelling decreased and the temperature dropped. Recovery was steady from this point on. The acute cutaneous lesions healed in fourteen days, leaving tiny atrophic areas. The atopic dermatitis was unchanged. The patient had been successfully vaccinated at the age of 2 years and had no known exposure to a recently vaccinated person. Eight and ten days before his acute infection he had been exposed to his older brother and father, both of whom had labial herpes. The patient himself had not experienced previous herpetic infection.

**CASE 3.**—E. B., a white woman aged 25, had had atopic dermatitis since childhood. At the time of onset of the present eruption she presented only a dry slightly scaling eczematoid eruption on the face, neck and cubital areas. On Feb. 11, 1946 she experienced burning and itching on the neck and face. A few hours later lentil-sized vesicles on an inflammatory base appeared. Swelling of the face, neck and eyelids and cervical lymphadenopathy followed. On admission to Christ Hospital on February 12 the temperature was 100.0 F. The leukocytes numbered 4,900, the erythrocytes 4,120,000, polymorphonuclear leukocytes 77 per cent, eosinophils 3 per cent, small lymphocytes 12 per cent and mononuclear cells 8 per cent. The hemoglobin measured 13 Gm. The urine was normal. An agent capable of provoking keratoconjunctivitis in rabbits was isolated from the cutaneous lesions and proved to be herpes. The patient was given 2 units of pooled plasma forty-eight hours apart, without apparent change locally or systemically. Penicillin wet dressings and, later, penicillin ointment were used topically. Thiamine and sodium

salicylate were given orally. Her temperature continued at 100.0 F. for eight days and then subsided. The lesions crusted; swelling disappeared, and the areas healed leaving a few tiny pits. The underlying atopic dermatitis showed little change from its status before the acute episode. The patient had been successfully vaccinated when a child, and a subsequent vaccination, in her "teens," had failed to take. She had for six days been exposed to her fiance, who had labial herpes. The eruption appeared five days after the last exposure. The patient was sure that she had not previously had herpetic infection.

Three weeks after the onset of the acute eruption typical labial herpes developed, one lesion on the upper and one on the lower lip. The lesions ran the usual course of labial herpes and disappeared in a few days. Seventeen days later red papules appeared on her forehead and in forty-eight hours spread over the whole face. Three days after the onset of the eruption the lesions were vesicular, lentil sized and umbilicated. Some of the lesions in this attack were small vesicopapules and did not form vesicles. The whole surface of the face and neck was erythematous. Discrete lesions on the chest and back, outside the confluent areas, had decided erythematous halos. The patient was again hospitalized. Her temperature was 101.2 F. The leukocytes numbered 5,750 and erythrocytes 5,000,000. The hemoglobin measured 14.5 Gm. The urine was clear. Penicillin wet dressings were applied locally. Thiamine and sodium salicylate were administered orally. One unit of pooled plasma was given intravenously, without apparent effect. On March 28 the leukocytes numbered 4,200 and on March 31, 5,000. She again experienced edema of the neck and cervical lymphadenopathy. After five days her temperature became normal and her herpetiform lesions cleared, leaving her atopic dermatitis somewhat reddened. She was discharged from the hospital on April 1. The atopic dermatitis subsided within a few days with soothing topical measures. Inoculation of material from the acute cutaneous lesions on a rabbit's cornea was inconclusive as to the presence of herpes virus.

CASE 4.—H. T., a white woman aged 23, had atopic dermatitis from 4 to 12 months of age. It recurred at 5 years of age, cleared in one and one-half years and recurred again for a period of two years at 13 years of age. She was first seen in July 1945 with atopic dermatitis, which had been present for the past year. The cutaneous involvement was generalized but was accentuated on the face, neck and flexure surfaces of the extremities. After treatment in Christ Hospital for two months the atopic dermatitis was brought under reasonable control. Subsequently, the course of the disease until the patient was readmitted to the hospital, April 25, 1946, was fluctuating. Periods of moderate exacerbation of the eruption alternated with periods during which the skin was relatively clear. Forty-eight hours prior to readmission, the patient complained of feeling drowsy and tired. She noted enlargement of the lymph glands of her neck. Twenty-four hours before readmission, the entire cutaneous surface became erythematous; she experienced fever, and vesicles appeared on her face and neck. On admission she presented an eruption that was generalized except for a few clear areas on her trunk and legs. The face, neck and arms were confluent involved. The lesions were lentil sized, umbilicated vesicles. The face and neck were edematous, and serum was oozing from the cutaneous lesions. A decided cervical lymphadenopathy was present. Discrete and grouped lesions, with inflammatory halos, appeared over the other areas of the body. The temperature was 105.0 F. The leukocytes numbered 4,000, polymorphonuclear leukocytes 90 per cent, eosinophils 1 per cent, basophils 1 per cent, small lymphocytes 4 per cent and mononuclear cells 4 per cent. The urine was normal except for a faint trace of albumin. An agent capable of pro-

voking keratoconjunctivitis in rabbits was isolated from the cutaneous lesions. Penicillin was administered topically and parenterally. She received 2 ampules of immune globulin intramuscularly daily. New lesions appeared in crops for five days, and the skin of the face, neck, chest, back and arms became covered with confluent oozing denuded areas. The temperature reached levels between 105.0 and 106.0 F. daily. Blood cultures were sterile. The leukocytes fell to 3,000 on April 26 and to 2,000 on April 27. "Pentnucleotide" N.N.R. and dextrose were given intravenously. The cutaneous lesions on the legs and thighs and some of those on the arms became crusted and were healing by May 1. On this day the patient became disoriented and irrational. She died on May 2 of respiratory failure. The patient had been successfully vaccinated at the age of 7 years, and two subsequent vaccinations had been unsuccessful. She had no history of preceding herpetic infection. For about ten days before the fatal disease developed she had been exposed to her fiance, who had labial herpes.

#### LABORATORY DATA

In the preceding reports it was stated that an agent capable of provoking keratoconjunctivitis in rabbits was obtained from the cutaneous lesions of 4 patients with Kaposi's varicelliform eruption. This agent was identified as herpes virus through host susceptibility, histologic studies of the lesions obtained in the host, cultural studies and filtration experiments. Neutralization tests were performed with homologous and heterologous strains of the virus and the patients' serums in order to establish a relationship of the agent to the disease. Cross immunity tests in mice and rabbits were made to show the relationship to a known strain of herpes simplex.

*Methods and Materials.*—*Animals:* Animals included in the various tests were rabbits, hamsters and mice. The mice were albinos of either sex, supplied by a local dealer. Mice weighing between 10 and 18 Gm. were used for the titrations, neutralization tests and routine passages. When injections were made peripherally, in order to obtain immune survivors, mice weighing approximately 22 Gm. were employed.

*Inoculums:* (a) Vesicular fluid was obtained by puncturing relatively fresh vesicles on the patients' skin with a sterile cataract knife. A cotton swab previously moistened with sterile isotonic solution of sodium chloride was lightly wiped over the area. The material was then used to rub onto the scarified cornea of a rabbit.<sup>8</sup>

(b) The nictitating membrane or a piece of the rabbit's cornea was removed as aseptically as possible, washed with several changes of sterile isotonic solution of sodium chloride and ground with alundum in about 1 cc. of isotonic solution of sodium chloride. The suspension was centrifuged at 1,500 revolutions per minute for a few minutes, and the clear supernatant fluid was used for inoculation of mice and cultures on blood agar plates. The supernatant and sediment were then mixed again, and a swab of the crude suspension was rubbed on the scarified cornea of another rabbit.

(c) The brains were removed aseptically from infected moribund mice, weighed and ground in a mortar with alundum to make a 10 or 20 per cent suspension.

8. Scarification of rabbits' corneas and intracerebral inoculations were performed while animals were under full ether anesthesia.

After centrifugation the supernatant was removed. Isotonic solution of sodium chloride was the diluent used for the routine cerebral mouse passages, and rabbit serum in isotonic solution of sodium chloride<sup>9</sup> was used for the titrations and neutralization tests. Occasionally, for storage in solid carbon dioxide, brain suspension was prepared in undiluted rabbit serum. For the maintenance of strains entire infected mouse brains were placed into "lusteroid" tubes and stored in solid carbon dioxide. When needed the frozen brain was dropped from the "lusteroid" into a mortar, while still frozen, and then triturated as described. It was observed that all strains of virus could be maintained in solid carbon dioxide for long periods. As a rule mice received 0.03 cc. of inoculum intracerebrally and amounts ranging between 0.1 cc. and 0.5 cc. intraperitoneally. Intracerebral titrations in mice gave LD<sub>50</sub> titers ranging between 2.5 and 5.0. Hamsters were given 0.06 cc. intracerebrally.

**Sterility Tests:** All tissues and tissue suspensions were routinely cultured on blood agar plates. During the early phases of the work various enrichment mediums as well as plain agar and nutrient broth were employed. Anaerobic cultures were included. No bacterial growth was obtained in any of the mediums, except for occasional contaminants that were encountered especially during the primary isolations.

**Filtration:** Freshly prepared 10 per cent mouse brain suspensions were centrifuged and put through Berkefeld "V" candles. The bacteria-free filtrates of all four strains of virus produced encephalitis in mice after intracerebral inoculation.

**Histologic Studies:** Pieces of rabbit cornea and nictitating membrane were fixed in Zenker's solution containing 5 per cent acetic acid and the sections stained with hematoxylin and eosin. Occasionally a mouse brain was cut longitudinally in half and sectioned in the same manner.

**Serums:** Serums were obtained during the acute phase of the disease and at least a month later, during the convalescent period in all patients except H.T. In addition, a third sample of blood was collected from E.B. approximately three months after the onset of her disease. All serums were removed from the clot as soon as possible and then stored in a box with solid carbon dioxide until used for neutralization tests.

**Neutralization Tests:** Twenty per cent suspensions of infected mouse brain were prepared each time. Decimal dilutions were made in rabbit serum in isotonic solution of sodium chloride, giving concentrations of 1 to 5, 1 to 50 and so forth up to 1 to 500,000 or 1 to 5,000,000. These when added to equal amounts (0.15 cc.) of undiluted test serums gave final concentrations of 1 to 10, 1 to 100 and so forth up to 1 to 1,000,000 or 1 to 10,000,000. The mixtures of virus dilution and serum were incubated in a water bath for two hours at 37 C. At the end of this time the mixtures were injected intracerebrally into groups of 4 or of 5 mice, which were observed daily for signs of involvement of the central nervous system and death over a period of twenty-one days. LD<sub>50</sub> titers were calculated according to the method of Reed and Muench,<sup>10</sup> and neutralization indexes were determined by the method described in "Laboratory Methods of the United States Army."<sup>11</sup>

9. Rabbit serum isotonic solution of sodium chloride consisted of rabbit serum which had been inactivated at 56 C. for one-half hour and made up to 10 per cent in isotonic solution of sodium chloride.

10. Reed, L. J., and Muench, H.: Simple Method of Estimating Fifty per Cent Endpoints, Am. J. Hyg. 27:493 (May) 1938.

11. Simmons, J. S., and Gentzkow, C. J.: Laboratory Methods of the United States Army, Philadelphia, Lea & Febiger, 1944, p. 591.

Known Strains of Herpes Virus: The H.F. strain of herpes virus<sup>12</sup> was used in most of the immunity tests. The P.A. strain, recently isolated from a patient with herpetic stomatitis, was used in a few of the early tests until the H.F. strain became available.

Disease in Animals: Mice succumbed with symptoms characteristic of herpetic encephalitis after intracerebral or intraperitoneal inoculation. Corneal scarification in rabbits was followed by the typical keratoconjunctivitis of herpes simplex and in many cases by encephalitis.

*Isolation of the J.M. Strain.*—The crusts and vesicular fluid obtained from J.M. were swabbed on both scarified corneas of rabbit 1. In twenty-four hours violent purulent keratoconjunctivitis was produced in both eyes. At this time the nictitating membrane and cornea of the right eye were removed aseptically and ground in isotonic solution of sodium chloride after representative pieces had been saved for histologic section. Subsequently, when tested for ocular immunity rabbit 1 was observed to be resistant to the P.A. strain of herpes virus.

The nictitating membrane of rabbit 1 was injected intracerebrally into mice and onto the scarified cornea of rabbit 2. This rabbit failed to react. However, the same material produced encephalitis in mice. The cornea of rabbit 1 was transferred to the scarified cornea of rabbit 3. Keratoconjunctivitis developed by the third day. On the seventh day, while the reaction still appeared at its height, the cornea of rabbit 3 was removed and passed to another rabbit, which failed to react. However, herpetic inclusions were readily demonstrated in the cornea of rabbit 3, and it was later shown to be immune to ocular scarification with the P.A. strain of herpes virus.

The brains of all except 1 mouse inoculated with the nictitating membrane of rabbit 1 were discarded because bacteria were observed. A suspension of brain from this mouse was frozen in solid carbon dioxide. Four months later it was thawed and divided into two parts. One part, about 0.5 cc., was left untreated. To the other part, which was approximately 3 cc., 2,500 units of penicillin contained in 0.25 cc. of isotonic solution of sodium chloride was added. Culture of the untreated portion yielded numerous colonies on a blood agar plate, whereas that portion treated with penicillin produced no growth. Both the treated and the untreated portions failed to elicit a response in the scarified corneas of a rabbit immune to the H.F. strain of herpes. On the other hand, passage of both portions to the scarified corneas of a normal rabbit (rabbit 4) evoked severe keratoconjunctivitis. Its nictitating membrane was removed on the third day and injected intracerebrally into 6 mice. Four died with signs of involvement of the central nervous system, while the 2 mice which did not die were resistant five weeks later to the

12. The H. F. strain of herpes simplex was supplied by Drs. P. K. Olitsky and J. Casals of the Rockefeller Institute for Medical Research, New York.

homologous J.M. strain of virus. The original penicillin-treated portion of the mouse brain suspension was injected intracerebrally into 6 mice. All showed signs of encephalitis; 1 died, and 4 were shown to be immune

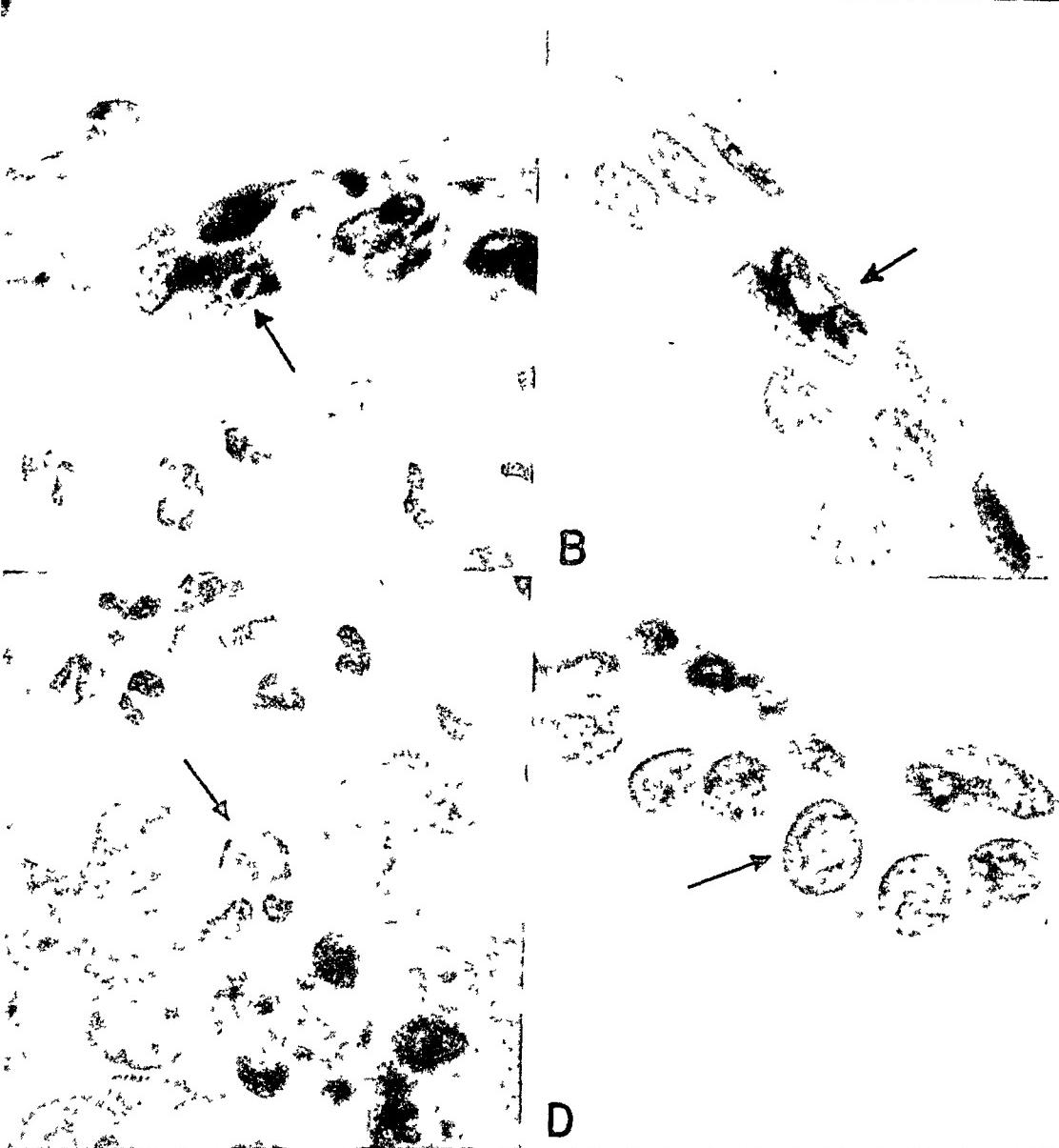


Fig. 2.—Intranuclear inclusions in rabbits' eyes. The sections are stained with hematoxylin and eosin. *A*, intranuclear inclusion in the epithelium of the cornea (case 1) ( $\times$  approximately 1,297). *B*, intranuclear inclusion in the epithelium of the cornea (case 2) ( $\times$  approximately 1,297). *C*, intranuclear inclusion in the epithelium of the cornea (case 3) ( $\times$  approximately 1,297). *D*, intranuclear inclusion in the epithelium of the iris (case 4) ( $\times$  approximately 1,297).

to herpes. The sixth was killed on the fourth day. Culture of its brain revealed no bacteria, and histologic section showed the presence

of herpetic inclusions. Intracerebral passage of its brain to mice produced convulsions and death between the second and sixth days. Continuous mouse brain passage shortened the period of incubation to as little as twenty-four hours and resulted in a hundred per cent mortality when 10 per cent brain suspensions were employed.

*Isolation of the F.R. Strain.*—Four small wet vesicles from the skin of patient F.R. were punctured and the contents taken up by a cotton swab and applied to the scarified corneas of rabbit 5. Keratoconjunctivitis developed in rabbit 5, and at seventy-two hours the cornea and nictitating membrane of the left eye were removed. Section of the cornea revealed herpetic inclusions in the epithelial cells. This rabbit was later observed to be immune to ocular infection with the P.A. strain of herpes. Further inoculation of another rabbit with the cornea and nictitating membrane did not produce any reaction. This rabbit was subsequently susceptible to the P.A. strain of virus. Passage of the ground-up nictitating membrane of rabbit 5 to 5 mice resulted in the death of 2 of them on the eighth and ninth days, respectively. Of the 3 remaining animals, 1 was eventually shown to be resistant to cerebral infection with the P.A. strain while another succumbed. The fifth mouse showed symptoms on the eleventh day. The strain obtained from its brain was maintained by continuous mouse brain passage.

*Isolation of the E.B. Strain.*—Material from cutaneous vesicles and also from the conjunctivas of patient E.B. was inoculated on both eyes of rabbit 8. On the second day when no reaction occurred, fresh material was obtained from a new crop of vesicles and both corneas of the rabbit were reinoculated, as were the corneas of rabbit 9. Severe keratoconjunctivitis developed in the 2 rabbits. Rabbits 8 and 9 were later shown to be immune to ocular infection with the H.F. strain. On the third day following the last inoculation the right cornea and nictitating membrane of rabbit 8 were removed. Section of the cornea showed the presence of eosinophilic intranuclear inclusions in the epithelial cells. The nictitating membrane of rabbit 8 was injected intracerebrally into 5 mice. In 1 encephalitis developed on the eighth day and in another on the tenth day. The brain of the latter was passed to other mice, and this strain was maintained for several passages. The remaining 3 mice were tested about a month later for cerebral immunity to the homologous E.B. strain. One was immune, and the other 2 succumbed.

*Recurrence of Eruption in Patient E.B.*—Material from the cutaneous lesions of E.B. was inoculated on the corneas of rabbit 10 in the usual manner. Only mild purulent conjunctivitis developed. Although herpetic inclusions could not be demonstrated in either the cornea or nictitating membrane and no disease was produced by cerebral inoculation into mice, the rabbit later resisted both ocular and cerebral

infection with the H.F. strain of herpes. The evidence is therefore inconclusive as to whether herpes virus was present in the lesions of the patient and as to whether this was a true recurrence of the disease.

*Isolation of the H.T. Strain.*—Swab 1: Material from the lesions of patient H.T. was inoculated on the cornea of 2 rabbits. One, a rabbit which was immune to the H.F. strain of virus, showed no reaction; the other, rabbit 11, showed a characteristic reaction in each eye. The left cornea and nictitating membrane were removed for section and passage on the third day. In the absence of any corneal epithelium no inclusions could be observed. A pool of the nictitating membrane and cornea was passed to rabbit 12 and the nictitating membrane alone to 6 mice. The rabbit, in which a lesion failed to develop, was subsequently susceptible to ocular infection with the H.F. strain. The mice all succumbed between the fifth and seventeenth days after showing signs of involvement of the central nervous system. Herpetic inclusions were demonstrated in sections of the brain of 1 mouse that died on the fifth day. This brain was used to maintain the strain of virus.

On the seventh day rabbit 11 began to show signs of involvement of the central nervous system. The entire right eye was removed and sectioned, and a herpetic inclusion body was observed in the iris. A 20 per cent suspension of the brain was made and injected intracerebrally into 7 mice. One of the mice succumbed on the eighth day, and its brain was used for further passage. The remaining 6 mice remained well and on a later date were shown to be not immune to the homologous strain of virus. A rabbit in which the 20 per cent brain suspension was injected intracerebrally had a febrile reaction of three days' duration and then recovered. Four weeks later when this animal's cornea was inoculated with the highly fatal H.F. strain of herpes only mild purulent keratitis developed.

Swab 2: Material for a second inoculation was obtained from patient H.T. the day before death. Keratoconjunctivitis developed in both eyes of the rabbit, and eosinophilic intranuclear inclusions were seen on section. This rabbit was resistant to ocular infection with the known H.F. strain later. Virus was demonstrated in the nictitating membrane by intracerebral subinoculation into 5 mice.

*Neutralization Tests.*—Two series of neutralization tests were performed. In the first series the patients' serums, obtained during both the acute and the convalescent phase of disease, were studied with regard to their neutralizing effect on the homologous strain of virus, and in the second series the neutralizing effect of the serums from 3 patients on the heterologous H.F. strain of virus was studied. The serum of a normal rabbit was used as a control.

In table 1 it can be seen that J.M. had no antibodies in the serum in the acute phase of the disease, while the serum drawn seven weeks

TABLE I.—Results in Mice (Neutralizing Antibodies) of Tests with Patients' Serums (0.03 cc. Injected Intracerebrally)

Source	Phase of Disease	Date	Homologous Virus Test												Heterologous (HF) Virus Test												
			Dilution						Dilution						Dilution						Dilution						
			10 <sup>-1</sup>	10 <sup>-2</sup>	10 <sup>-3</sup>	10 <sup>-4</sup>	10 <sup>-5</sup>	LD <sub>50</sub> Titer	10 <sup>-1</sup>	10 <sup>-2</sup>	10 <sup>-3</sup>	10 <sup>-4</sup>	10 <sup>-5</sup>	LD <sub>50</sub> Titer	10 <sup>-1</sup>	10 <sup>-2</sup>	10 <sup>-3</sup>	10 <sup>-4</sup>	10 <sup>-5</sup>	LD <sub>50</sub> Titer	10 <sup>-1</sup>	10 <sup>-2</sup>	10 <sup>-3</sup>	10 <sup>-4</sup>	10 <sup>-5</sup>	LD <sub>50</sub> Titer	
Normal rabbit	.....	.....	.....	1/4†	2/4	3/4	0/4	4.0	.....	.....	4/4	4/4	3/4	2/4	1/4	5.0	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....
J. M.	Acute	11/29/45	1/4	1/4	1/4	1/4	1/4	4.0	1	.....	4/4	4/4	1/4	0/4	0/4	3.7	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....
J. M.	Convalescent	1/18/46	1/1	1/3	0/4	0/4	0/4	0.8—	1600+	x1600+	1/4	0/4	0/4	0/4	0/4	2.5	3.0	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....
Normal rabbit	.....	.....	.....	4/5	1/5	2/5	0/5	3.5	.....	.....	1/4	1/4	3/4	1/4	0/4	3.5	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....
F. R.	Acute	1/6/46	5/5	4/5	2/5	1/4	...	2.8	5	.....	1/4	1/4	3/4	1/4	0/4	3.5	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....
F. R.	Convalescent	2/6/46	5/5	1/5	0/5	...	1.7	60	x12	3/4	1/4	0/4	0/4	0/4	2.5	3.0	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....
Normal rabbit	.....	.....	.....	3/4	2/4	0/4	0/4	2.8	.....	.....	4/4	4/4	2/4	0/4	0/4	3.5	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....
E. B.	Acute	2/12/46	0/1	0/1	0/4	0/4	0/4	0.5—	200+	.....	2/4	2/4	0/4	0/3	0/3	3.5	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....
E. B.	Convalescent	3/22/46	1/3	0/1	0/4	0/4	0/4	0.7—	125+	x1	2/4	3/4	0/4	0/4	0/4	3.0	100	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....
E. B.	Recurrent	5/16/46	1/4	0/4	0/4	0/4	0/4	0.7—	125+	x1	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...	...
Normal rabbit	.....	.....	.....	4/4	2/4	0/4	0/4	4.0	.....	.....	4/4	4/4	2/4	0/4	0/4	3.5	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....
H. T.	Acute	1/26/46	1/4	1/4	1/4	0/4	0/4	3.5	3	.....	4/4	4/4	3/4	0/4	0/4	3.0	100	.....	.....	.....	.....	.....	.....	.....	.....	.....	.....

\* Neutralization Index =  $\frac{LD_{50} \text{ titer test serum}}{LD_{50} \text{ titer normal rabbit serum}}$ 

† The numerator shows the number of mice that died; the denominator shows the number of mice inoculated.

later, during his convalescence, showed a neutralization index of more than 1,600. The serum of F.R. in the acute phase of the disease showed a neutralization index of 5, and the index increased to 60 in the convalescent phase a month later. The neutralization index of the serum of E.B. in the acute phase of the disease was more than 200, and no difference was observed in samples of serum drawn five weeks and three months later, respectively, both indexes being more than 125. No neutralizing antibodies were observed in the serum of H.T., which was drawn just before death.

The neutralization index of the various serums against the heterologous H.F. strain increased during convalescence to a comparable extent. The serum of J.M. during convalescence increased only sixteen-fold, as compared to the sixteen hundredfold increase with the homologous strain. The F.R. serum increased tenfold, and the E.B. serum

TABLE 2.—*Cerebral Resistance of Immunized Mice to the H.F. Strain of Herpes Simplex*

Experiment Number	H. F. Suspension Used	Previous Inoculation		Result
		Strain	Route	
1	Rabbit brain (1%)	F. R.....	Intraperitoneal	1/22*
			Intracerebral	0/3
		E. B.....	Intraperitoneal	0/3
			Intracerebral	0/2
2	Mouse brain (1%)	Controls....	.....	6/6
		J. M.....	Intracerebral	0/6
		H. T.....	Intraperitoneal	1/4
		Controls....	.....	10/10

\* The numerator shows the number of mice that died; the denominator shows the number of mice inoculated.

showed a negligible increase in protective capacity during convalescence, which duplicates the results with the homologous strain. The H.T. serum was not available for neutralization tests with the H.F. strain.

*Cross Immunity Tests in Animals.*—Final proof of the identity of the infectious agents was established by performing several series of resistance tests in mice, hamsters and rabbits. Mice immunized with the human strains of virus were tested against the H.F. strain, and, conversely, mice immunized with the H.F. strain were tested against the various human strains of virus. A group of hamsters resistant to the H.T. strain also was tested for intracerebral resistance to the H.F. strain. Finally, the experiments were concluded by testing recovered rabbits for ocular immunity to either the P.A. or the H.F. strain of virus.

*Cerebral Resistance of Mice to the H.F. Strain:* In the first experiment (table 2) mice which had received either the F.R. or E.B. strains

TABLE 3.—*Cerebral Resistance of H.F. Immune Mice to Human Strains of Herpes Simplex*

Experiment Number	Strain of Herpes *	Group of Mice	Result
1	J. M.	H. F. immune.....	0/4†
		Controls.....	4/4
2	F. R.	H. F. immune.....	0/4
		Controls.....	4/4
3	H. T.	H. F. immune.....	0/18
		Controls.....	14/14

\* Freshly prepared 10 per cent mouse brain suspensions.

† The numerator shows the number of mice that died; the denominator shows the number of mice inoculated.

Note.—In these experiments the H. F. immune mice had survived a previous cerebral challenge with the H. F. strain.

TABLE 4.—*Ocular Resistance of Rabbits to Herpes Simplex*

Experiment Number	Date of Test, Virus Used	Inoculation of Cornea		Reaction	Result
		Strain	Date		
1	1/28/46, P. A. 10% mouse brain	Nonspecific	12/ 4/45	Keratoconjunctivitis, CNS *	
		Nonspecific	12/ 4/45	Keratoconjunctivitis	
		Nonspecific	1/17/46	Keratoconjunctivitis, CNS	
	J. M. J. M. F. R.	J. M.	11/20/45	None	Immune
		J. M.	11/30/45	None	Immune
		F. R.	1/ 5/46	None	Immune
	4/18/46, H. F. 10% rabbit brain	Nonspecific	11/18/45	Keratoconjunctivitis, CNS, D9 †	
		Nonspecific	11/21/45	Keratoconjunctivitis, CNS, D9	
		Nonspecific	3/15/46	Keratoconjunctivitis, CNS, D12 ‡	
		J. M.	1/28/46	None	Immune
		F. R.	1/28/46	None	Immune
		F. R.	2/ 1/46	None	Immune
2	E. B. E. B. E. B. §	E. B.	2/12/46	None	Immune
		E. B.	2/14/46	None	Immune
		E. B. §	3/27/46	None	Immune
	5/20/46, H. F. 10% mouse brain	Nonspecific	.....	Keratoconjunctivitis, CNS, D8	
		Nonspecific	5/16/46	Keratoconjunctivitis, CNS, D9	
		J. M.	4/29/46	None	Immune
		H. T.	5/ 2/46	None	Immune
	H. T. ¶	H. T. ¶	5/ 4/46	Mild keratoconjunctivitis	Immune

\* Involvement of the central nervous system.

† The rabbit died on the ninth day.

‡ The rabbit died on the twelfth day.

§ This rabbit had received material from the recurrent lesions of E. B.

¶ The rabbit died on the eighth day.

¶ This rabbit had received intracerebral injection.

of virus were subjected to an intracerebral injection of a 1 per cent H.F. rabbit brain suspension. All except 1 were solidly immune. In the second experiment a 1 per cent suspension of H.F.-infected mouse brain was employed on mice immune to J.M. and H.T. strains. All except 1 were resistant, thus demonstrating good cross immunity. It may be pointed out that mice which had previously survived a cerebral challenge, regardless of the strain of herpes virus employed, were solidly immune, whereas after previous intraperitoneal injection an occasional mouse succumbed to cerebral inoculation. All control mice in these experiments died.

**Cerebral Resistance of Mice Immune to the H.F. Strain to Human Strains of Virus:** Freshly prepared 10 per cent mouse brain suspensions were used in these experiments, and the results are listed in table 3. Mice rendered immune to the H.F. strain were resistant to the J.M., F.R. and H.T. strains of virus injected intracerebrally. There were no survivors among the normal controls.

**Resistance to the H.F. Strain of Hamsters Immune to the H.T. Strain:**—A group of 4 hamsters survived intracerebral injection of the H.T. strain. Later they were all immune to cerebral inoculation with the H.F. strain, while 4 normal controls died.

**Ocular Resistance of Rabbits to Strains of Herpes Simplex:** Rabbits that had recovered from ocular infection with the four human strains of virus were tested for ocular immunity. Three separate experiments were made and the results are shown in table 4. In the first experiment a 10 per cent suspension of P.A. mouse brain was used. It can be seen that 2 rabbits given injections of J.M. strain and 1 rabbit given the F.R. strain were resistant. In the remaining two tests the H.F. strain became available, and the results showed that good cross immunity was developed in rabbits that had received one of the J.M., F.R., E.B. or H.T. strains of virus. Animals which had been inoculated on the cornea with unrelated materials acted as controls, and all succumbed.

#### COMMENT

Herpes virus was readily isolated by transfer to a rabbit's cornea from the cutaneous lesions of 4 patients with Kaposi's varicelliform eruption. The infectious agent was obtained in some instances many days after the onset of the disease and once was isolated from the same patient twice, the second time six days after the first. Inclusion bodies were observed in the rabbit's eye on the second day and up to the seventh day after scarification. Intracerebral inoculation of mice with material from infected rabbit's eyes seldom gave universally positive results, but at least in four instances it proved a successful method of transfer when inoculation of single rabbits failed. Antibodies against the homologous herpes virus were absent during the acute phase of the illness

in 3 patients and present in 1. One patient showed a decided rise in titer in the serum in the convalescent period, 1 a slight rise and 1 no rise either after her first illness or after the possible recurrence of the disease. As the fourth patient died, serum was obtained only in the acute period and no antibody was observed. Cross immunity was demonstrated between all four strains and the known H.F. strain and another strain obtained locally from a patient with herpetic stomatitis.

The first suggestion that the disease described by Kaposi might be caused by herpes virus came from the work of Seidenberg,<sup>13</sup> who used material obtained from 2 patients of Esser's<sup>14</sup> to inoculate rabbits. Keratoconjunctivitis developed in the rabbits, and they were subsequently immune to herpes but not to vaccine virus. The excellent work of Wenner<sup>15</sup> in 1944 established the fact that the virus of herpes simplex is almost certainly the causative agent of the disease. He isolated strains of a filtrable agent from the vesicular fluid of each of 3 infants and from the brain of 1 of them at necropsy and identified the strains as closely related to, if not identical with, the virus of herpes simplex. Serums obtained from 1 patient one month, two months and five months after the onset of illness neutralized herpes virus, but at seven months the antibodies had disappeared. In the serum of a second infant antibodies were observed at eight and at twenty-three days. Blattner and his associates<sup>16</sup> shortly thereafter reported the recovery from the lesions of a child of a strain of herpes virus by the use of mice and embryonated hens' eggs. Antibodies, absent on the seventh day of illness, were present on the fifteenth and thirtieth days. The patient was 1 of a group of 5 patients reported by Lane and Herold.<sup>15</sup> Serums obtained from the 4 other patients during convalescence and from 1 more patient in Chicago were tested by Blattner for the presence of antibodies. He observed antibodies in the serums of 2 patients of Lane and Herold and in the serum of the patient from Chicago. The serums of the remaining 2 patients were negative. Some doubt existed as to whether 1 of the patients had Kaposi's varicelliform eruption. Lane and Herold gave two possible interpretations of the lack of antibody in the serum of the other patient, who had presented a typical picture of the disease: The disease might have been produced by an unrelated strain of virus, or, in view of the fact that the sample was taken twelve months after recovery, antibodies might have disappeared from the blood stream.

13. Seidenberg, S.: Zur Aetiologie der Pustulosis vacciniformis acuta, Schweiz. Ztschr. f. Path. 4:398, 1941.

14. Esser, M.: Ueber eine kleine Epidemie von Pustulosis varioliformis acuta, Ann. prædiat. 157:156, 1941.

15. Lane, C. W., and Herold, W. C.: Kaposi's Varicelliform Eruption: Report of Five Cases, Arch. Dermat. & Syph. 50:396 (Dec.) 1944.

Barton and Brunsting<sup>6b</sup> were the first to record the isolation of the herpetic virus from the lesions of an adult. Lynch and his associates<sup>6d</sup> described 4 cases, in 2 adults and 2 infants. Both children were exposed to herpes in their parents, and 1 adult had labial herpes two days prior to his eruption. The fourth patient, aged 54 years, gave no history of exposure. From the lesions of this patient they obtained the virus of herpes simplex. Antibodies were present in the serum of this patient at three days, and there was no change in the titer seventy-five days later. Jaquette and his co-workers<sup>6e</sup> added 1 more proved case in an infant. Although the child had been exposed to a vaccinated sibling, it was the herpetic virus which was isolated from the lesions. Antibodies to herpes absent at the onset were elaborated by the patient during convalescence. Ebert, in a discussion of Lynch's paper, stated that on reexamination of sections of the cornea of a rabbit in which keratitis developed when it was inoculated with material from a patient with Kaposi's eruption, the typical inclusion bodies of the herpes group were seen. He also observed inclusion bodies in the lesions taken from the skin of the patient. Inclusion bodies have been found in the cutaneous lesions of herpes labialis and genitalis.<sup>16</sup> Apparently this is the only instance in which they have been seen in Kaposi's varicelliform eruption.

It is as yet impossible to say whether the herpetic cutaneous eruption is, like herpetic stomatitis, a manifestation of primary herpetic infection.<sup>17</sup> The relative frequency of the disease in infancy and the high fever and prostration of the patients point to such a conclusion. The serums of most of the infants and of some of the adults have been shown to be lacking in antibodies against herpes early in the course of the disease and to develop a rise in titer during convalescence. However, antibodies have been demonstrated in some patients early in the disease; in those patients no rise has subsequently occurred. One patient apparently suffered a relapse<sup>6a</sup> and 1, reported here, a recurrence. The presence of virus in the late lesions was not conclusively demonstrated in either instance. If it is established that Kaposi's varicelliform eruption is a manifestation of primary herpes there will be at least two disease pictures of "herpetic fever": one, the usual herpetic stomatitis and the second, the rarer generalized cutaneous eruption occurring usually on an eczematous base.

16. van Rooyen, C. E., and Rhodes, A. J.: Virus Diseases of Man, London, Oxford University Press, 1940, p. 150.

17. Dodd, K.; Johnston, L. M., and Buddingh, G. J.: Herpetic Stomatitis, *J. Pediat.* **12**:95 (Jan.) 1938. Burnet, F. M., and Williams, S. W.: Herpes Simplex: New Point of View, *M. J. Australia* **1**:637 (April 29) 1939.

## SUMMARY

Four cases of Kaposi's varicelliform eruption are reported, of which 3 were in adults. One patient had a clinical relapse of the disease thirty-nine days after the first attack, and between these attacks, on the twenty-second day after the first episode, she had labial herpes. Each of these patients had been in contact from five to ten days preceding the onset of Kaposi's varicelliform eruption with 1 or more persons who had labial herpes. The 3 adults had been successfully vaccinated at an earlier date. None of the 4 patients had any known exposure to vaccine virus preceding the development of Kaposi's varicelliform eruption. Penicillin, plasma and immune globulin failed to influence the course of the disease. A filterable agent recovered from the cutaneous lesions of each of these 4 patients was shown by histologic methods and appropriate cross immunity tests in animals to be a strain of herpes simplex virus. An increase in antibodies during convalescence was demonstrated in 2 patients. In 1 fatal case in an adult there were no antibodies in the acute stage.

These 4 cases add corroborative evidence to that already accumulated that Kaposi's varicelliform eruption may be produced by infection with herpes virus in persons having atopic dermatitis. The recovery of the herpes virus distinguishes this disease from eczema vaccinatum, which is due to infection with the vaccine virus in persons having atopic dermatitis.

NOTE.—While this manuscript was in the process of preparation an additional case of Kaposi's varicelliform eruption in a 20 month old infant (male) was diagnosed.<sup>7</sup> Material from the patient's lesions produced keratoconjunctivitis in rabbits, and herpetic inclusions were readily demonstrated in sections of rabbit cornea. A virus recovered from the cutaneous lesions was shown by appropriate immunity tests to be a strain of herpes virus. Antibodies which were absent in the serum in the acute phase of the disease were shown to develop during convalescence. Work is still in progress.

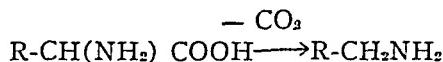
Dr. Roy L. Kile aided in the management of the patients, and Mr. Joseph Homan of the Department of Medical Art prepared the photographs.

## ASCORBIC ACID IN THE TREATMENT AND PREVENTION OF POISON OAK DERMATITIS

DAVID H. KLASSON; M.D.

BROOKLYN

THE STUDY of dermatitis venenata due to poison oak (*Rhus diversiloba*) was undertaken, while I was a member of the armed forces, with the assumption that the manifestations observed in the disease were probably due, as in other allergic states, to an overproduction of histamine and other such monoamines in the body tissues. The hypothesis was carried still further, based on the probability that the irritating factor in poison oak (lobinol, a volatile oil isolated by McNair<sup>1</sup>) first decomposes the protein molecules in the cutaneous tissues into a-amino acids by a process similar to that of the proteolytic enzymes in digestion. These amino acids may further be decomposed not according to the normal method of deamination and oxidation but by losing carbon dioxide from the carboxyl group (decarboxylation) with the formation of a corresponding alkyl amine, as:



Various studies have shown that the monoamines, such as tyramine and histamine, have a powerful physiologic action even in minute quantities. Histamine, when injected into the body, promptly causes increased arterial tension by its direct action on the arteriolar wall, and later a fall in blood pressure results from increasing capillary permeability. This would probably explain the hyperemia seen in early manifestations of poison oak dermatitis and the subsequent vesiculation of the cutaneous tissue.

An idea was conceived that since one of the physiologic actions of ascorbic acid is to maintain vascular tone, especially of the vascular endothelium, ascorbic acid might counteract the toxic actions of alkyl amines like histamine. An experimental study which I did on rabbits proved this to be true. With this in mind and the knowledge of the harmless effect of ascorbic acid on the human body, a study was undertaken in the treatment and prevention of poison oak dermatitis.

Three hundred and eighty patients with dermatitis venenata due to poison oak were observed and treated by my associates and me. Of

1. McNair, J. B.: *Rhus Dermatitis from Rhus Toxicodendron, Radicans and Diversiloba (Poison Ivy): Its Pathology and Chemotherapy*, Chicago, University of Chicago Press, 1923.

these, 126 received treatment with ascorbic acid, and the results were favorable. Some of the results were startling, however; obstinate cases of the disease were encountered which necessitated longer treatment, with eventual improvement. The period of treatment was definitely reduced. The average period of treatment for the 126 patients was five days, the shortest two days and the longest ten days (table 1). It was noted that the earlier treatment was initiated after exposure the quicker and more favorable was the recovery. The ascorbic acid was given only to those patients who presented manifestations of moderately severe or severe disease. Patients with mild dermatitis were treated with the usual topical application of calamine lotion or tincture of ferric chloride.

All patients who were treated were ambulant. Few with severe dermatitis had to be hospitalized, and hospitalization in these cases was primarily due to the lack of ascorbic acid at one time or another. It should be remarked that during the period from June to August 1943,

TABLE 1.—Number of Days Required for Treatment of Each Patient in 126 Cases

Number of Patients	Days
15.....	2
28.....	3
11.....	4
38.....	5
11.....	6
12.....	7
7.....	8
4.....	10

when more than two thirds of the 380 patients were treated, only 6 were hospitalized. In 1 of these a secondary infection had developed.

In the determination of prophylaxis against poison oak dermatitis, two groups of men (24 in each group) who were sensitive to the plant were employed as test cases. Each group was divided into two sections, 12 men in each section. During the period of exposure to poison oak, those in one section took the prescribed prophylactic dose of ascorbic acid and those in the other did not. Those who took the prophylactic dose of ascorbic acid did not contract the disease when exposed, while a large percentage of those who were not given the daily dose of ascorbic acid did contract poison oak dermatitis, ranging from mild to severe (tables 2 and 3). The dose which is felt to be adequate for protection ranges from 150 to 300 mg. daily and can be taken in tablet form, in divided doses. This daily dose must be taken one day prior to exposure, every day during exposure and at least twenty-four to forty-eight hours after exposure.

The dosage varied somewhat and depended on the severity of the dermatitis. However, it is felt that the maximum daily dose in any

case is 600 mg. of ascorbic acid. The dose was divided into two or three portions during the day and given at intervals of four to six hours. Sterile ampules of ascorbic acid solution, 100 mg. each, were employed. It is believed that a more concentrated solution or a preparation of a

TABLE 2.—*Results of Prophylaxis Against Poison Oak\* in Group 1†*

Section A ‡		Section B §	
Case No.	Resultant Dermatitis	Case No.	Resultant Dermatitis
1.....	None	13.....	Mild
2.....	None	14.....	Mild
3.....	None	15.....	Severe ..
4.....	None	16.....	Moderate
5.....	None	17.....	Moderate
6.....	None	18.....	Moderate
7.....	None	19.....	None
8.....	None	20.....	None
9.....	None	21.....	Mild
10.....	None	22.....	None
11.....	None	23.....	Moderate
12.....	None	24.....	Moderate

\* The patient in each case gave a history of being highly susceptible to poison oak.

† Investigation was made along the California coast line.

‡ These patients were given 300 mg. of ascorbic acid by mouth daily, in divided doses of 100 mg. each, during a period of exposure of three days and were checked on the fifth day for signs of poison oak dermatitis.

§ These patients received no ascorbic acid, were exposed for three days and were checked for signs of poison oak dermatitis on the fifth day.

TABLE 3.—*Results of Prophylaxis Against Poison Oak\* in Group 2†*

Section A ‡		Section B §	
Case No.	Resultant Dermatitis	Case No.	Resultant Dermatitis
25.....	None	37.....	Moderately severe
26.....	None	38.....	Moderate
27.....	None	39.....	Severe
28.....	None	40.....	Moderate
29.....	None	41.....	Severe
30.....	None	42.....	Moderate
31.....	None	43.....	Severe
32.....	None	44.....	Severe
33.....	None	45.....	Moderate
34.....	None	46.....	Moderate
35.....	None	47.....	Moderately severe
36.....	Moderate	48.....	Moderate

\* The patient in each case gave a history of being highly susceptible to poison oak.

† Investigation was made along the California coast line.

‡ These patients were given 150 mg. of ascorbic acid by mouth daily, in divided doses of 50 mg. each, for a period of seven days. Exposure began on the second day after the initiation of prophylaxis and lasted for five days. On the seventh day they were examined for signs of dermatitis.

§ These patients received no ascorbic acid, and the period of exposure and time of examination were as for section A.

|| The patient in this case did not follow the prescribed procedure.

water-in-oil emulsion of ascorbic acid, for prolonged action would serve the purpose more satisfactorily. The best route of injection seems to be the intramuscular one, for if given intravenously the ascorbic acid is eliminated too rapidly from the blood stream. The subcutaneous method

is too painful. It is also advisable under certain conditions to give the ascorbic acid in tablet form by mouth as a supportive to the injection. When ascorbic acid is given orally, twice the amount that is employed by injection should be given. This, however, does not completely replace the injections. When vesiculation is present topical application of calamine lotion is recommended as a supportive measure.

At no time were deleterious effects from the drug observed. In fact, patients usually said that they felt well while taking the ascorbic acid.

The drug may be given up to 1 Gm. or more daily. The first sign of improvement is a reduction in itching. This may come about two to four hours after the first injection. This improvement wears off in a few hours if no further ascorbic acid is given. That is probably due to the fact that the ascorbic acid is rapidly eliminated from the system. Furthermore, in no instance were there noted any inflammatory reactions, which are at times seen when extracts of poison oak preparations are given.

#### SUMMARY

Despite the small number of patients treated and the diverse reactions of different persons to poison oak and to treatment, which make it difficult for one to reach concise conclusions, it is felt that ascorbic acid is capable of combating the disease. Through its physiologic action it has possibilities in preventing the contraction of poison oak dermatitis, and it promptly alleviates the symptoms of the already contracted disease. The best results are usually obtained in those persons who present symptoms of edema, as of the eyelids and genitals.

NOTE.—The author was awarded the Commendation Ribbon by the War Department for meritorious service, while a member of the 125th Infantry, Northern California Sector, in 1943. The commendation stated "Colonel (then Captain) Klasson conducted an investigation and study on the cause and cure of poison oak, the results of which were applied with commendable success within the regiment, thereby contributing greatly to the health and comfort of the command."

80 Clarkson Avenue.

## Clinical Notes

### TROPICAL LICHENOID DERMATITIS

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The submission of this note is prompted by a recent article by Nelson.<sup>1</sup> During 1944 and the early part of 1945, patients presenting the syndrome later described by Bagby<sup>2</sup> and Nisbet<sup>3</sup> were frequently seen in the Italian theater of war, and their cases were discussed by Nelson with the dermatologists mentioned in his first reference. I had over 50 cases at 102 South African General Hospital in Bari and was able to see several more at the neighboring New Zealand General Hospital. These facts alone would not justify the further report of a disease, which has now been adequately described, but I feel that the following points might be of historical interest:

1. In 1935, while I was stationed in Soroti, Uganda, British East Africa, I saw a colleague's wife with a cutaneous disease which resembled acute lichen planus, which diagnosis had been made by Dr. J. H. Sequeira (then practicing in Nairobi, Kenya Colony). This woman and her husband were, to my knowledge, the first persons in Uganda to take "atebrin" (quinacrine hydrochloride)<sup>4</sup> for the suppression of malaria instead of the standard quinine compound.

2. In February 1944, during a discussion at the Section of Dermatology of the Royal Society of Medicine, Major Hellier and Dr. Roxburgh between them mentioned 3 cases of atypical lichen planus in soldiers from West and North Africa.<sup>5</sup> They stressed the occurrence of facial lesions, and it was the appearance of this "spectacle frame" dermatitis in many of the patients seen by Nelson and me that suggested to my mind a common factor between the case herein mentioned, 3 cases from West and North Africa and the numerous cases which were being seen in the Italian theater. The only common factor which occurred to me was the taking of quinacrine hydrochloride, and it was then that I first suggested that this drug might be of causative significance. Apparently, the same idea occurred inde-

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1. Nelson, L. M.: Unusual Dermatoses Simulating Lichen Planus and Lichen Cornens Hypertrophicus: Report of Six Cases, Arch. Dermat. & Syph. 55:12 (Jan.) 1947.

2. Bagby, J. W.: A Tropical Lichen Planus-like Disease, Arch. Dermat. & Syph. 52:1 (July) 1945.

3. Nisbet, T. W.: A New Cutaneous Syndrome Occurring in New Guinea and Adjacent Islands, Arch. Dermat. & Syph. 52:221 (Oct.) 1945.

4. The original German product is referred to here.

5. Hellier and Roxburgh, A. C., in discussion on Dowling, G. B.: Erythematous Lichen Planus, Proc. Roy. Soc. Med. 37:410 (June) 1944.

pendently to Peterkin.<sup>6</sup> The War Office, however, vetoed the proposed publication of these cases.<sup>3</sup> I had previously submitted to the editor of this journal a short article on a case of sensitization to actinic light which was precipitated by quinacrine hydrochloride and had mentioned that this was apparently unconnected with a series of cases of lichen planus attributable to the drug. In view of the veto by the War Office I asked the editor not to publish the report.

#### CLINICAL COMMENT

Two points might conveniently be mentioned here: 1. In none of the cases observed by me were there lesions of the glans penis, although the oral mucosa was frequently involved. This would be a remarkable fact were the disease true extensive lichen planus. Bazemore and his colleagues<sup>7</sup> did not mention lesions of the glans penis in over 400 cases of this disease which were seen by them. This fact might be of importance in the differential diagnosis. 2. In 1 case seen by me the eruption began as large bullae, which appeared on apparently normal skin. Only after these bullae had ruptured and healed did lichenoid lesions appear, on both previous sites of bullae and previously unaffected areas.

#### SUMMARY

A historical retrospect of tropical lichenoid dermatitis includes a case seen by me in 1935. Attention is drawn to the absence of lesions of the glans penis.

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6. Peterkin, cited by Nelson.<sup>1</sup>

7. Bazemore, J. M.; Johnson, H. H.; Swanson, E. R., and Hayman, J. M.: Relation of Quinacrine Hydrochloride to Lichenoid Dermatitis (Atypical Lichen Planus), Arch. Dermat. & Syph. **54**:308 (Sept.) 1946.

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#### ' SULFONAMIDE SENSITIVITY AND PROPHYLAXIS AGAINST VENEREAL DISEASE

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The soldier in the recent conflict was exposed to sulfonamide drugs in many forms in his appearances at the unit dispensaries. The various forms of toxic cutaneous reactions to these drugs have been adequately dealt with by Cohen, Thomas and Kalisch,<sup>1</sup> Weiner,<sup>2</sup> Ellis<sup>3</sup> and others, and the following case is reported in order to show that small amounts of the drug may set off irritating and extensive reactions.

Prophylaxis against venereal disease as practiced in the army was of several types. The "station" type of prophylaxis at the dispensaries consisted of local

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1. Cohen, M. H.; Thomas, H. B., and Kalisch, A. C.: Hypersensitivity Produced by the Topical Application of Sulfathiazole, J. A. M. A. **121**:408 (Feb. 6) 1943.

2. Weiner, A. L.: Cutaneous Hypersensitivity to Topical Application of Sulfathiazole, J. A. M. A. **121**:411 (Feb. 6) 1943.

3. Ellis, F. A.: The Potential Danger of the Topical Use of Sulfathiazole, South. M. J. **37**:493 (Sept.) 1944.

use of soap and water, intraurethral instillation of strong protein silver solution and local application of ointment of mild mercurous chloride. For areas where station facilities were not convenient the soldier was furnished with an individual chemical prophylactic kit. The earlier types of these packets contained two tubes of silver trinitrophenolate and ointment of mild mercurous chloride; another type was of silver preparation. Later a one tube kit was issued which contained 15 per cent sulfathiazole and 30 per cent ointment of mild mercurous chloride. The latter type was responsible for a typical toxic cutaneous reaction in the case described.

#### REPORT OF A CASE

A white soldier, aged 24 years, was first seen in the dispensary in August 1943, for a complaint of penile sores following sexual contact. A diagnosis of chancroid was made, and the treatment included the use of 7.5 grains of sulfathiazole three times daily. To the patient's knowledge he had not previously had any sulfonamide drugs. Treatment was continued until the afternoon of the following day, when there appeared generalized edema of the face, which closed the eyelids, pruritus, erythema and formation of vesicles about the lips and chin and edema of the hands. The vesicles became enlarged, coalesced and contained moderate amounts of a clear fluid. No other symptoms were noted. The lesions rapidly disappeared after treatment with the drug was discontinued. In November 1944 the patient reported to another dispensary, with a urethral discharge subsequently diagnosed as acute gonorrhreal urethritis. Treatment was instituted with 2 Gm. of sulfathiazole, since the patient made no mention of his sensitivity, and within four hours the same phenomena appeared as on the previous occasion: edema, erythema and formation of blebs about the face and lower lip. Penicillin was substituted, and the patient rapidly improved. He was cautioned for a second time about his sensitivity. In May, 1945, following another contact, acute gonorrhreal urethritis was again diagnosed, and 500,000 units of penicillin were required before the discharge ceased. On July 14 the patient had another sexual contact, and twenty minutes later he used an individual chemical prophylactic kit of the type described as containing sulfathiazole. After five to six hours the following reaction was noted: pruritus of the face, edema of the lips and the soft tissues about the eyes and vesicles about the upper lip and cheeks. No local lesions were noted about the genitals, and in this instance the symptoms were not as severe as on the previous occasions. Recovery was complete in thirty-six hours with no treatment. Questioning revealed that on numerous other occasions when chemical prophylaxis was used the method was always of the "station" type or with the two tube silver packets (trinitrophenolate and ointment of mild mercurous chloride). After this last episode patch tests were made with 5 per cent sulfathiazole and sulfadiazine ointments, and each elicited a strong erythematous reaction. Minute vesicles were noted with sulfathiazole. Ointment of mild mercurous chloride gave no reaction.

#### CONCLUSIONS

This case exemplifies the fact that after sensitization to a sulfonamide compound once occurs later exposures to the same drug can produce identical reactions, regardless of whether the drug is taken orally or applied to a cutaneous or mucous surface. Abramowitz<sup>4</sup> and Lane<sup>5</sup> have indicated that the commonest offender

4. Abramowitz, E. W.: Hazards of the External Use of Sulfonamide Compounds, Arch. Dermat. & Syph. **50**:289 (Nov.) 1944.

5. Lane, C. W.: Observations on the Topical Application of the Sulfonamides, South. M. J. **38**:125 (Feb.) 1945.

is sulfathiazole in topical application, although the other members of the group are almost equally frequently a cause. Certainly the use of the drugs internally for more serious illnesses poses a sufficiently large problem for the prescriber of these drugs. It would seem to be a questionable policy to have a chemical prophylactic kit containing sulfonamide compounds available to the public for mass and indiscriminate use.

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#### TREATMENT OF SCABIES WITH DDT (DICHLORODIPHENYLTRICHLOROETHANE)

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War and scabies go hand in hand, and so the detection and treatment of scabies in returning soldiers are important. The period of incubation of scabies is about three weeks. Although the disease may have been contracted in India, China, France or Italy, it may not be evident until after the soldier has landed in the United States because of the speed of modern travel. The zeal to see his sweetheart, wife or family may overshadow the "itch," and thus the soldier innocently spreads the infection to a large number of persons by various means, such as riding buses and trains, sleeping in hotels and private homes and sexual intercourse. Though the number of cases seen in an army general hospital nowhere compares with that seen overseas or in large camps, there are enough to constitute a therapeutic problem. Incidentally, it appeared to me that there were proportionately many more cases from the Mediterranean and European theaters than from the Pacific and allied theaters of operations. During a six month period of observation 307 cases of scabies were diagnosed at Oliver General Hospital; 80 per cent of the patients had no symptoms or eruption until after their arrival in the zone of the interior.

There are numerous methods of treating scabies. Each gives good results but may have certain undesirable qualities. The use of salves is messy and uncomfortable. Benzyl benzoate is effective, but about 10 to 15 per cent of patients treated with it have untoward reactions, particularly dermatitis venenata. With practically all methods there is about 5 to 10 per cent relapse after treatment. About the same percentage of patients are careless in following a prescribed treatment. It therefore appeared that there was still room for improvement in the treatment of scabies. Though others may have used the method to be reported, no articles to date have appeared on the subject.

A prescription for a lotion containing DDT (dichlorodiphenyltrichloroethane), a lotion being considered more desirable than a salve in that it can be applied more freely and quickly, was devised which it was hoped would be harmless and without side effects. This was done hesitatingly, since it had been reported that DDT was harmful to the skin and particularly injurious if applied in an oily solution and since it was reported to be easily absorbed and capable of causing changes in the blood cells and the viscera. A 7 per cent mixture of DDT in equal parts of xylol, ether and liquid petrolatum was prepared, and I used it on myself as a repellent for mosquitoes for two weeks. Since there were no unpleasant effects, it was given to patients to be applied to the body once a

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From Oliver General Hospital, Augusta, Ga.

day for three days, and the first 10 patients were studied for changes in the blood and urine. Since no changes were seen in red or white cells, platelets, hemoglobin or urine more persons were treated both at this installation and at several larger camps. No ill effects were reported, and in better than 95 per cent of the patients the pruritus disappeared after the first application. Though not all the cases could be followed there was only about 6 per cent failure after the three day treatment. It appears that if the clothing and bed linens could have been washed in a DDT solution the recurrence of the scabies could have been still further reduced. Treatment with DDT in the form of inert powder or salve was not attempted. Again, some of the relapses were due to the fact that many of the patients were treated while in arm, leg or partial body casts, and the parasites were still under the casts after treatment. The desire to relieve them of some of their nocturnal pruritus was the reason for treatment. A group of patients with scabies was treated with only the mixture of xylol, ether and liquid petrolatum, but they failed to respond to treatment. The average patient used about 240 to 300 cc. of solution.

#### SUMMARY AND CONCLUSIONS

Soldiers have returned and are still returning from overseas, infested with scabies. Because of this, physicians should be alert to a higher incidence of scabies in the civilian population. In a six month period, 307 patients with scabies at Oliver General Hospital have been successfully treated with a 7 per cent solution of DDT (dichlorodiphenyltrichloroethane) in equal parts of xylol, ether and liquid petrolatum. The lotion is applied once a day for three days, and the average patient uses between 240 and 300 cc. of fluid. The usual procedures of changing and cleaning clothes and bedding are recommended. Spraying or rinsing the clothes in a 5 to 7 per cent DDT solution might further decrease the incidence of relapse or infestation. No untoward symptoms, such as dermatitis venenata or changes in the blood elements or urine, were observed. No doubt, as with all drugs, there will be some untoward reactions, but to date none has been noted. Ninety-five per cent of the patients treated did not experience pruritus after the first treatment. Six per cent of the patients required further courses of treatment. Though this is not a large series of cases and many could not be followed for long periods of time to permit my drawing any final and definite conclusions, I believe that DDT will figure importantly in the treatment of scabies.

623 Doctors Building.

## Obituaries

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### WALTER THOMPSON GARFIELD, M.D.

1882-1947

Walter Thompson Garfield, one of the older members of the New England Dermatological Society, died following a cerebral hemorrhage on May 30, 1947. He leaves his widow and two sons, Leonard Dwinell and Philip Nickerson.

Garfield was born in Pembroke, Mass., on Feb. 8, 1882, the son of Leonard Dwinell and Leonice Thompson Garfield. His early education was obtained at the Cambridge Latin School, from which he graduated in 1902. He received the degree of A.B. from Harvard College in 1906 and the degree of M.D. from the Medical School in 1909.

After internship at the Boston City Hospital he practiced general medicine from 1912 to 1917. He served as Assistant Superintendent of the Bailey Hospital at Lincoln, Neb., and at St. Elizabeth's Hospital at Washington, D. C. He served in World War I from 1917 to 1919 as a captain in the Medical Corps. After his return he practiced dermatology and syphilology and was connected with the Boston City Hospital and the Boston Dispensary as a visiting physician.

He became Chief of the Dermatological Service of the Boston City Hospital during the recent war and was connected with Tufts College Medical School as a teacher from 1921 to 1944, when he became Professor of Dermatology and Syphilology.

He was a diplomate of the American Board of Dermatology and Syphilology and a member of the American Academy of Dermatology and Syphilology and of the New England Dermatological Society, of which he was a past president. He was Chief of the Outpatient Clinic in Dermatology, Cambridge City Hospital, and a consulting physician at the Norwood and Long Island Hospitals at the time of his death.

He was a member of Mt. Olivet Lodge, Ancient Free and Accepted Masons, from 1902 to 1947 and a thirty-second degree member of the Albert Pike Consistory of Washington, D. C., from 1918 to 1927. He was a member of the Utopian Club and past president of the Sachem Council Boy Scouts of America.

Garfield was of a retiring and modest nature, but friendly with those with whom he was associated in his professional life. He served in the various dermatologic clinics with kindly consideration for the underprivileged patients from the poorer districts served by these clinics.

In the clinic he was always punctual in his attendance and carried out his duties with diligence and thoroughness.

Dr. Garfield was a keen clinical observer and a good diagnostician, and his discussion of cases was always interesting. He made many contributions to dermatologic literature over the years and presented a variety of interesting cases at the clinical meetings of the New England Dermatological Society.

Dr. Garfield will be missed by the New England Dermatologists and particularly by his patients who recognized in him a skilful and kindly physician.

WILLIAM P. BOARDMAN, M.D.

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## News and Comment

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### GENERAL NEWS

**Application for Space in Scientific Exhibit at Next Annual Session.—** The Scientific Exhibit for the next annual session of the American Medical Association, to be held in Chicago in June 1948, is under the direction of Dr. Francis W. Lynch, 1466 Lowry Medical Arts Building, St. Paul. Those who desire to present an exhibit should write directly to Dr. Lynch for application for space.

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